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Mobile phone applications and self-management of diabetes: a systematic review with meta-analysis, meta-regression of 21 randomized trials, and GRADE

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Mobile phone applications and self-management of diabetes: a systematic review with meta-analysis, meta-regression of 21 randomized trials, and GRADE

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ABSTRACT

AIMS: To evaluate the growing evidence base of mobile phone applications for the self-management of type 1 and 2 diabetes mellitus. Then, to investigate the impact of app functions as moderating effects, including the impact of health care professional (HCP) feedback incorporated in the apps.

MATERIALS AND METHODS: A systematic review with meta-analysis, meta-regression and GRADE of the evidence. Relevant randomized controlled trials that were published between 1 January 1996 and 1 May 2017 and reported either HbA1c or severe hypoglycemic episodes as outcomes were searched in five databases: Medline, CINAHL, Cochrane Library, Web of Science, and Embase.

RESULTS: 1550 participants from 21 studies were included in the review. For type 1 diabetes, a significant 0.49% reduction in HbA_{1c} was seen (95%CI 0.04 to 0.94; I^2=84%), with unexplained heterogeneity and a low GRADE of evidence. For type 2 diabetes, using diabetes apps was associated with a mean reduction of 0.57% in HbA_{1c} (95%CI 0.32 to 0.82, I^2=77%). The results had severe heterogeneity that was explained by the frequency of HCP feedback. In studies with: no HCP feedback, a mean reduction of 0.24% (95% CI -0.02 to 0.49; I^2=0%); low frequency, mean reduction of 0.33% (95% CI 0.07 to 0.59; I^2=47%); and high frequency a mean reduction of 1.12% (95%CI 0.91 to 1.32; I^2=0%), with high GRADE of evidence.

No evidence was found of excess severe hypoglycemic episodes associated with diabetes apps (seven studies).

CONCLUSIONS: There is evidence that diabetes apps improve glycemic control in type 1 diabetes patients. A reduction of 0.57% in HbA1c was found in type 2 diabetes patients. However, HCP involvement is critical functionality to achieve clinical effectiveness. A cost-effectiveness study is needed to evaluate whether diabetes apps should be used routinely.

INTRODUCTION

In the past three decades, the number of people with diabetes worldwide has risen from 153 million in 1980 [1] to 382 million in 2013 [2], and is expected to rise to 592 million by 2035 [2]. The high prevalence of diabetes gives rise to the increased global healthcare costs on diabetes and, more importantly, its complications. The estimated health expenditure on diabetes worldwide increased from 548 billion US dollars in 2013 to over 612 billion US dollars in 2014 [3], imposing a huge economic burden to healthcare systems.

Nevertheless, there are overwhelming evidence that intensive glycated hemoglobin (HbA_{1c}) control can significantly reduce the risk of diabetes complications [4, 5]. But nowadays, the percentage of diabetes patients achieving the recommended HbA_{1c} target remains low [6, 7]. The importance of patients' self-management in achieving HbA_{1c} level of below 6.5% is well-recognized. Traditional diabetes self-management education (DSME) that aimed to improve diabetes self-management has shown to be associated with approximately 0.5% reductions in HbA_{1c} [8, 9]. However, the wide implementation of these self-management strategies is unrealistic in current over-burdened healthcare systems, as these strategies are historically resource-intensive and requires time from healthcare professionals (HCPs) and patients.

Diabetes mobile phone applications (diabetes apps) is a newly emerging technology for diabetes self-management. Due to its ubiquitous, cheap, interactive, and dynamic health promotion [10], diabetes apps may provide effective diabetes self-care by supporting diabetes patients in all the self-care behaviors and overcome the weakness of the current self-management strategies at the meantime. Our previous systematic review demonstrated that diabetes apps are effective in

controlling HbA_{1c} in type 2 diabetes patients [10], this conclusion was supported by three later systematic reviews [11-13]. However, there is still uncertainty on whether diabetes apps are effective in the self-management of type 1 diabetes, and which aspects of the apps are associated with better self- management. There is current debate to what extent the effect of diabetes apps on HbA_{1c} should be attributed to Health Care Professionals (HCP) [14].

The primary objective of this study is to determine the effectiveness and safety of the apps, and secondary objectives are to establish which features are likely mediating effects.

MATERIALS AND METHODS

Literature searching, selection criteria and data extraction

This study is an update of a systematic review following a pre-specified protocol and follows the PRISMA statement and checklist (PROSPERO reg. no. CRD42017067774). We searched relevant peer-reviewed studies published between June 1st, 2015 and May 1st, 2017 in five electronic databases: Medline, CINAHL, Cochrane Library, Web of Science, and Embase. The following terms and medical subject headings (MeSH) were used: mobile, mHealth, cell phones, cellular phone, smartphone, app, mobile applications, iphone, phone, diabetes mellitus, T2DM, T1DM, IDDM, NIDDM, DM, T1D, T2D, or MODY (Supplementary Table 1). The references of the included studies were hand searched to identify additional articles.

The inclusion and exclusion criteria used were: ⩾18 years old participants with type 1 or type 2 diabetes; the studies adopted randomized controlled trials (RCTs) design and reported HbA1c or severe hypoglycemic episodes as an outcome; the control group in the study received usual care

without any telehealth interventions. We define severe hypoglycemic episodes as any hypoglycemic episodes that require third-party assistance. For data extraction, participant demographics, study design considerations, and context were extracted from each included study (Supplementary tables 2 and 3). Corresponding authors were contacted to provide missing data, and where necessary, we used statistical methods to impute missing data [15, 16]. Literature searching, screening (including rescreening of previous search results for hypoglycemic episodes) and data extraction were conducted by two reviewers independently (CH and QX). Any disagreements were resolved by discussion with a third reviewer (JYL).

Risk of bias (RoB) assessment

The nine Cochrane RoB domains were categorized as 'low risk of bias', high risk of bias, or 'unclear' of each study [17]. Risk of bias will be independently evaluated by two authors (CH and SD) and any discrepancies in bias coding were resolved by a third reviewer (BC). Studies were classified with a high RoB if they determined as having a high RoB for both blinding and incomplete outcome data domains. If all domains were a low RoB the study was described with a low RoB, and unclear if a combination of low and unclear domains.

Data analysis and synthesis

The primary outcome is HbA_{1c}, and secondary outcome is severe hypoglycemic episodes. For the primary outcome, we used the inverse variance random effects model [18] to pool mean differences (MD) in HbA_{1c} changes from baseline or post-intervention HbA_{1c} for type 1 and type 2 diabetes studies separately [18]. The I^2 statistic was used to assess and quantify heterogeneity. When substantial heterogeneity was found (I^2>50%), we explored the source of heterogeneity using

subgroup analysis and meta-regression. For the secondary outcome, DerSimonian & Laird random-effects model [18] was used to carry out the pooling of risk ratios (RR) with the estimate of heterogeneity being taken from the Mantel-Haenszel model [19].

For cluster randomized controlled trial, effect size abstracted from an analysis that properly accounts for the cluster design is preferred [17]. Otherwise, an effective sample size will be used instead: $N_{effective}$= N/(1+(m−1)*ICC) (m: number of observations per cluster, ICC: intracluster correlation coefficient) [20], where parameter ICC was calculated from one of the included cluster randomized controlled studies [21]. All the statistical analyses were conducted using STATA (version 14.1) and Comprehensive Meta-Analysis (version 3).

Subgroup analyses and meta-regression

Subgroup analyses by HCP intensity were carried out for both type 1 and type 2 diabetes studies to explain heterogeneity. Random-effects meta-regressions were further carried out for type 2 diabetes studies to explore the factors that may influence the efficacy of apps on glycemic control. We applied a modification to the variance of the estimated coefficients as suggested by Knapp and Hartung [22] and used the residual maximum likelihood (REML) method to estimate between-study variance [23]. Univariable meta-regression analyses by length of the study follow up, baseline HbA_{1c} levels, and ages of the participants were carried out first. We then conducted multivariable meta-regression analyses to investigate what functions of the apps could influence HbA_{1c} control after adjusting for the predictors that found to be statistically significant ($p<0.05$) in the univariable meta-regressions. In the multivariable meta-regression analyses, Tau^2 was used to reflect

between-study variance while I^2-residual was calculated to reflect residual variation due to heterogeneity.

Sensitivity analyses and publication bias

For the primary outcome we removed studies with: a high RoB; had missing data imputation; and studies conducted on mixed participants. When 10 or more studies were pooled, we used funnel plot to visually inspect publication bias.

RESULTS

The literature search in five databases resulted in 4467 records, plus 5211 records identified on June 2015. Thirty-two manuscripts (21 studies) were included and 116 were excluded (Figure 1). In the 21 included studies [21, 24-43], three studies enrolled both type 1 and type 2 diabetes patients, of these, two studies provided additional data and could be included in both type 1 and type 2 syntheses [32, 34], and the third study included predominantly type 2 diabetes patients (>90%) so was classified as type 2 [30]. In total, 1550 participants were included in the meta-analysis, of which 516 were type 1 diabetes patients (average 35.3 ys old and 18.4 years of diabetes duration) and 1034 were type 2 diabetes patients (average 55.2 years old and 9.5 years of diabetes duration) (Supplementary Table 2). The median follow-up period is 6 months (range 3-9 months) and 6 months (range1.5-12 months) in type 1 and type 2 diabetes studies respectively.

INCLUDE FIGURE 1 HERE

One type 1 diabetes study [42] and three type 2 diabetes studies [30, 31, 33] were at high RoB, while the risk of bias in the remaining studies was unclear (Supplementary Figure 1 and 2). Studies with a high RoB were largely due to: blinding; use of fixed permuted-block randomization (in open-label trials); and high loss to follow up.

A total of 19 diabetes apps were assessed in 21 included studies, of which, four apps were assessed in type 1 diabetes patients, 12 in type 2 diabetes patients and three in both type 1 and type 2 diabetes patients. We examined diabetes apps in the following nine domains of functionality: self-monitoring tasks supported, data entry method, CHO/insulin bolus calculator, medication adjustment support, real-time personalized feedback (automated feedback provided by apps), structured display (display of blood glucose and other self-monitoring data), HCP feedback, frequency of HCP feedback and other functionalities (Supplementary Table 3). We further categorized HCP feedback into three groups according to the frequency of HCP feedback: no HCP feedback (did not support or provide additional HCP feedback in the intervention group), low frequency HCP feedback (when necessary or less than or equal to once per month) and high frequency HCP feedback (more than once per month). Among type 1 diabetes apps, two apps aimed to help patients with insulin bolus calculation and the others were designed to improve self-management by providing automated feedback or HCP feedback. None of type 1 diabetes apps supported real-time personalized feedback while wireless self-monitoring data transmission was supported in only one apps. As for HCP feedback, it was provided in four apps, with the frequency ranging from once per week to once per month. On the contrary, majority of the type 2 diabetes apps were designed to support diabetes self-management by providing personalized feedback on self-monitoring data (blood glucose, physical activity et al.). Besides, wireless data transmission and real-time personalized feedback was supported in

approximately half of the apps. In terms of HCP feedback, four studies of diabetes apps had no HCP feedback. In the remaining 12 studies of diabetes apps, seven provided low frequency HCP feedback and five had high frequency HCP feedback.

For primary outcome, seven studies on type 1 diabetes reported controversial results. After pooling, we found a mean reduction of 0.49% in HbA_{1c} that favored the intervention (95% CI 0.04 to 0.94; P=0.03, Figure 2), (hereafter, the reported values always refer to absolute reduction in HbA_{1c}), but exhibited considerable heterogeneity (I^2 = 84%), which was partially explained by HCP feedback (Figure 2). The differences between the subgroups were insignificant (P=0.26). We conducted two sensitivity analyses. Removing one study with incomplete data [43] reported an insignificant reduction of 0.49% (95% CI -0.04 to 1.01). When one study with high RoB was removed [42], the mean reduction decreased to 0.35% (95% CI -0.11 to 0.81). The level of evidence by GRADE is low, downgraded due to blinding and imprecision.

For type 2 diabetes, five studies reported statistically significant HbA_{1c} reduction that favored the apps, nine studies found improvements in HbA_{1c} but did not reach statistical significance, and two studies did not find any difference between the intervention and control groups. The pooled results indicated that compared with control, using diabetes apps was associated with a mean reduction of 0.57% in HbA_{1c} (95% CI 0.32 to 0.82; P < 0.01; Figure 3). Although these results exhibited significant heterogeneity (I^2 = 77%), it was explained by the HCP intensity (Figure 3). Studies with no HCP feedback reported a mean reduction of 0.24% (95% CI -0.02 to 0.49), whereas studies included low and high frequency HCP feedback had mean reductions of 0.33% (95% CI 0.07 to 0.59) and 1.12% (0.91 to 1.32) respectively. The level of evidence by GRADE for diabetes apps is high, based on downgrading for blinding but upgrading for dose-response.

For type 2 diabetes studies, three sensitivity analyses were conducted. Removing studies [30, 31, 33] with high risk of bias resulted in a mean reduction of 0.56% (95% CI 0.28 to 0.84). Exclusion of one study [30] that enrolled both type 1 and 2 patients reported a mean reduction of 0.57% (95% CI 0.30 to 0.83). Finally, we removed one study with incomplete data [29] and the mean reduction did not change distinctly (0.53%, 95% CI 0.28 to 0.79). There is no indication of publication bias in Supplemental Figure 3.

Although seven studies looked at severe hypoglycemic episodes [27, 28, 31, 36, 39-41], only one type 1 diabetes study [41] reported a total of four episodes of severe hypoglycemic in the intervention and control groups (one in the intervention group and three in the control group). Therefore, pooling of severe hypoglycemic episodes was not conducted as planned.

INCLUDE FIGURE 2 AND FIGURE 3 HERE

Meta-regression analysis

In the univariable meta-regression analyses (Supplementary Figure 4), we found a statistically significant relationship between baseline HbA_{1c} levels and effect size (P=0.02), suggesting the reduction in HbA_{1c} was likely to increase with the baseline HbA_{1c} levels. We also found that mean ages of the participants was inversely associated with effect size, indicating studies with younger participants may report larger effect size compared with trials with older participants (P=0.03). As for study length, its relationship to effect size was not statistically significant (P=0.82).

Based on the results from single covariate meta-regressions, we conducted series of multivariable meta-regressions that adjusted for ages and baseline HbA_{1c} values respectively. After adjusting for baseline HbA_{1c} levels, we found a significant dose-response relationship between HCP feedback and

effect size (P=0.02, Tau^2=0.04, I^2-*res*=37.22%, Supplementary Figure 5). This dose-response relationship remained to be significant when we adjusted for mean ages of the participants (P=0.01, Tau^2=0.05, I^2-*res*=45.85%). As for the other functionalities of the diabetes apps, their effect on glycemic control was insignificant in both models (Supplementary Figure 6).

DISCUSSION

This systematic review updated the body of evidence of diabetes apps to improve glycemic control in the self-management of diabetes. A total of 21 studies were included in this review, of which 8 studies were newly identified. For type 1 diabetes, a statistically significant reduction in HbA1c that favored the use of diabetes apps is reported for the first time. The results reaffirmed that apps for type 2 diabetes help with self-management, but also demonstrated a HCP dose-response with HbA_{1c}. The magnitude of the effect in the diabetes apps group with a highest level of HCP was higher than that in our previous meta-analysis [10].

Compared with three recent similar meta-analysis [11-13], the strengthens of our meta-analysis are most updated searching of the literatures, strict following of a registered protocol, exclusion of studies conducted on participants aged <18 years old and studies that used other kinds of electronic devices. Furthermore, out analysis were conducted separately for type 1 and type 2 diabetes patients. One of the novel findings of our review is that we reported a statistically significant reduction in HbA_{1c} among type 1 diabetes patients for the first time. Although previous reviews also revealed that diabetes apps that incorporated HCP feedback may be more effective, their conclusions are based on subgroup analysis and omit the potential effect of confounders. In our review, we used multivariable

meta-regression analyses to adjust for potential confounders and revealed a significant dose-response relationship between HCP feedback and HbA_{1c} reduction, which makes our conclusion more robust.

Nevertheless, our study has some limitations. Firstly, for the purpose of obtaining detailed information on the diabetes apps, we restricted the review to published articles, which may introduced publication bias. Due to the characteristics of the diabetes apps interventions, double-blind study design is not applicable, which raised the issue of high risk of ascertainment bias in all the included studies. Meanwhile, the assessment of risk of bias of included studies was inadequate for some domains, due to the lack of important information in some of the studies. Fourthly, the covariates included in the meta-regression models were study level data rather than patient level data, making our findings vulnerable to the ecological fallacy. Finally, because of insufficient numbers of studies, we were not able to investigate interactions between different functionalities of the apps.

Although the results in type 2 diabetes were associated with significant heterogeneity, it was significantly decreased after we stratified the studies by HCP intensity. The residual heterogeneity is acceptable for complex interventions like diabetes apps. The results from univariable meta-regressions suggested that baseline HbA_{1c} levels was a significant mediator for the effect of diabetes apps. The positive association between baseline HbA1c levels and reductions in HbA_{1c} is anticipated and accordant with findings in other diabetes researches [44, 45], as patients with higher baseline HbA1c levels generally have poorer glycemic control and are therefore more likely to benefit from interventions. The inverse linear relationship between mean ages of the participants and reductions in HbA_{1c} agrees with our previous hypothesis that younger patients were more likely to benefit from the use of diabetes apps [10]. Since it has been reported that older patients were less

interested in the use of diabetes apps [46], it is plausible that diabetes apps is less effective among older patients. However, there is no convincing external evidence supporting such hypothesis [47], and future researches need to investigate into this relationship more deeply. Our results revealed no significant association between follow-up duration and this finding is also supported by four studies, in which the HbA_{1c} reductions in the intervention groups kept stable at different follow-up visits [31, 33, 34, 38]. However, whether the effect of diabetes apps can sustain for a longer period of time (>1 year) is still largely unknown.

Results from multivariable meta-regressions statistically confirmed the hypothesis that the effect of diabetes apps in glycemic control is largely attributed to the effect of HCPs [12]. Although diabetes apps is projected to increase patients' self-efficacy and promote behavior change through features like reminder and real-time personalized feedback [14, 48], the effect of sole use of diabetes apps is likely to be small. There are two possible explanations for this finding. First, vast majority of the apps were not based on behavior change theory and had little impact on influencing lifestyle choice of the patients. Second, due to the limitations of technology, automated feedback can only provide limited support on self-management. Compared with diabetes apps with low frequency HCP feedback, those with high frequency feedback have significantly larger effect size. We speculate this difference is not only the result of different HCP intensity, but also the result of different types of HCP feedback. Among the four studies with high HCP intensity, all of them provided medication adjustment support. Whereas in the eight studies with low HCO intensity, medication adjustment support from HCPs was included in less than half of the studies. Our speculation is consistent with the findings from previous meta-analysis investigating other diabetes telemedicine interventions and diabetes quality improvement strategies [45, 49]. Therefore, we believe it is medication adjustments

support that plays a crucial role in the effect of HCP feedback. Based on these results, we postulate two main mechanisms behind the effects of diabetes apps on HbA_{1c} reduction (Supplementary Figure 7): (a) HCP feedback provide patients with medication adjustments and lifestyle modifications support (b) Self-monitoring using apps facilitates the HCP feedback.

For studies on type 1 diabetes, although we found a statistically significant reduction of 0.49%, the result was not robust and had some heterogeneity. Compared with the very low level of evidence we reported previously [10], the current level of evidence was rated up to low by GRADE, meaning future research is likely to change the estimate. It is notable that only one type 1 diabetes apps supported automatic data uploading functionality, therefore, we encourage more diabetes apps that include this functionality to be designed for type 1 diabetes patients.

Although there is some indication that the use of diabetes apps is associated with no excess severe hypoglycemia episodes, current evidence for the safety of diabetes apps is scarce. Future studies of diabetes apps should pay more attentions to the safety issues, especially for apps with bolus calculator functionality [50].

In recent years, the enthusiasm for diabetes apps is increasing with the worldwide smartphone usage rate. The purpose of our findings is not to dampen such enthusiasm, but to highlight the gaps in current diabetes apps and suggest future researches in this area. The population-wide implementation of diabetes apps need the support from both clinicians and payers. For clinicians, their primary consideration is not only the clinical effect of using diabetes apps for diabetes patients, but more importantly whether the time spent on adapting the technology and sending feedback justify the perceived benefit [51]. Hence, for future researches, we appeal that the intensity and types of HCP

feedback should always be reported with enough detail, so that clinicians can have a more comprehensive look at the study results. In order to fulfil HCPs' needs, future diabetes apps need to reduce dependencies in HCP feedback. We suggest that future diabetes should be underpinned by behavioral principles and diabetes self-management guidelines and incorporate gamification elements [52] and social medial function [46]. As for payers, cost-effectiveness of the intervention is their primary concern. Future investigators should consider conducting a comprehensive economic evaluation that takes into account both the direct and indirect cost of the diabetes apps. Meanwhile, investigators need to pay more attentions to evaluating the safety of diabetes apps. Furthermore, the long-term effects (>1 year) of diabetes apps are still unknown and need to be investigated in more pragmatic observational studies.

Conclusion

This systematic review and meta-regression reveals a robust 0.57% reduction in HbA_{1c} for diabetes apps compared with usual care in type 2 diabetes. However, this reduction in HbA_{1c} is largely dependent on the effect of health care professionals, which highlights the importance of comprehensive economic evaluation and developing more effective apps in the future. As for type 1 diabetes, we found a statistically significant reduction in HbA_{1c} that supported the use of diabetes apps, but the level of evidence was low. There is some indication that using diabetes apps will not increase the risk of severe hypoglycemic episodes. But the evidence is limited and more studies are needed.

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A transparency declaration: The manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Legends to figures

Figure 1—PRISMA flowchart of included studies

Figure 2: Pooled type 1 diabetes studies of HbA1c comparison of apps vs. control (subgroup by HCP feedback)

Figure 3: Pooled type 2 diabetes studies of HbA1c comparison of apps vs. control (subgroup by HCP feedback)

Figure 1

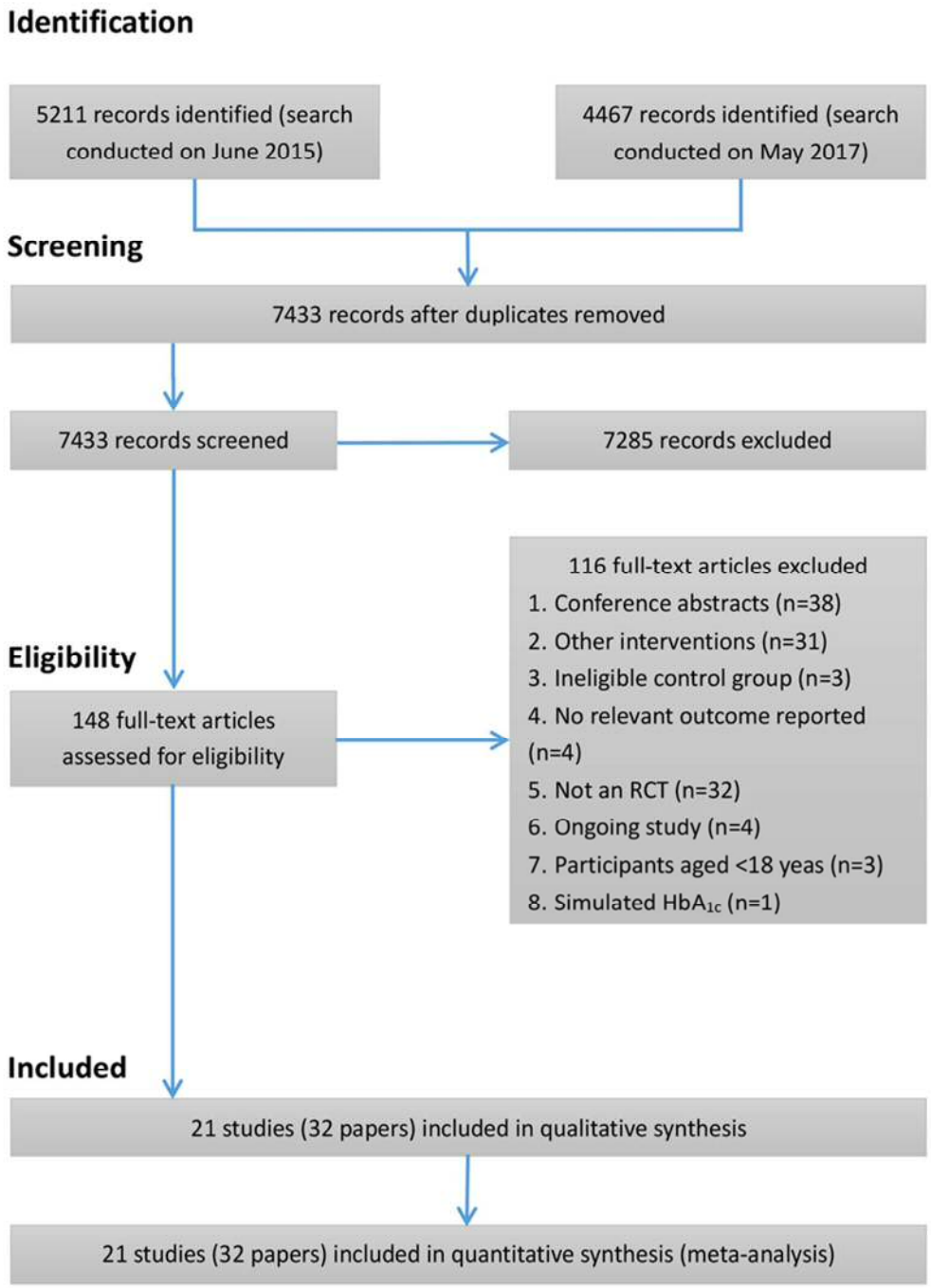
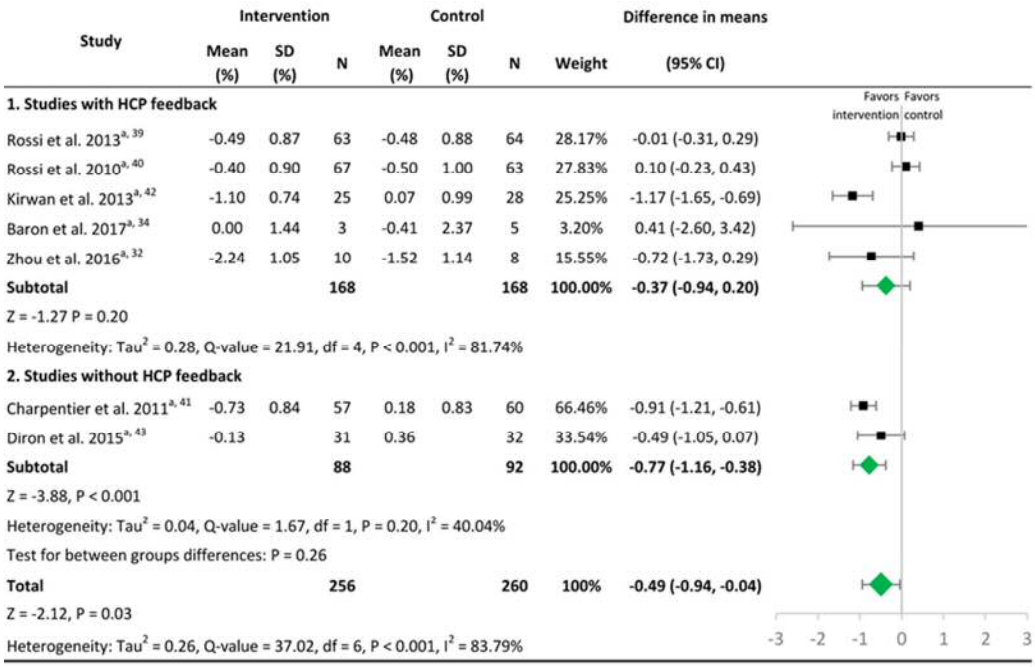
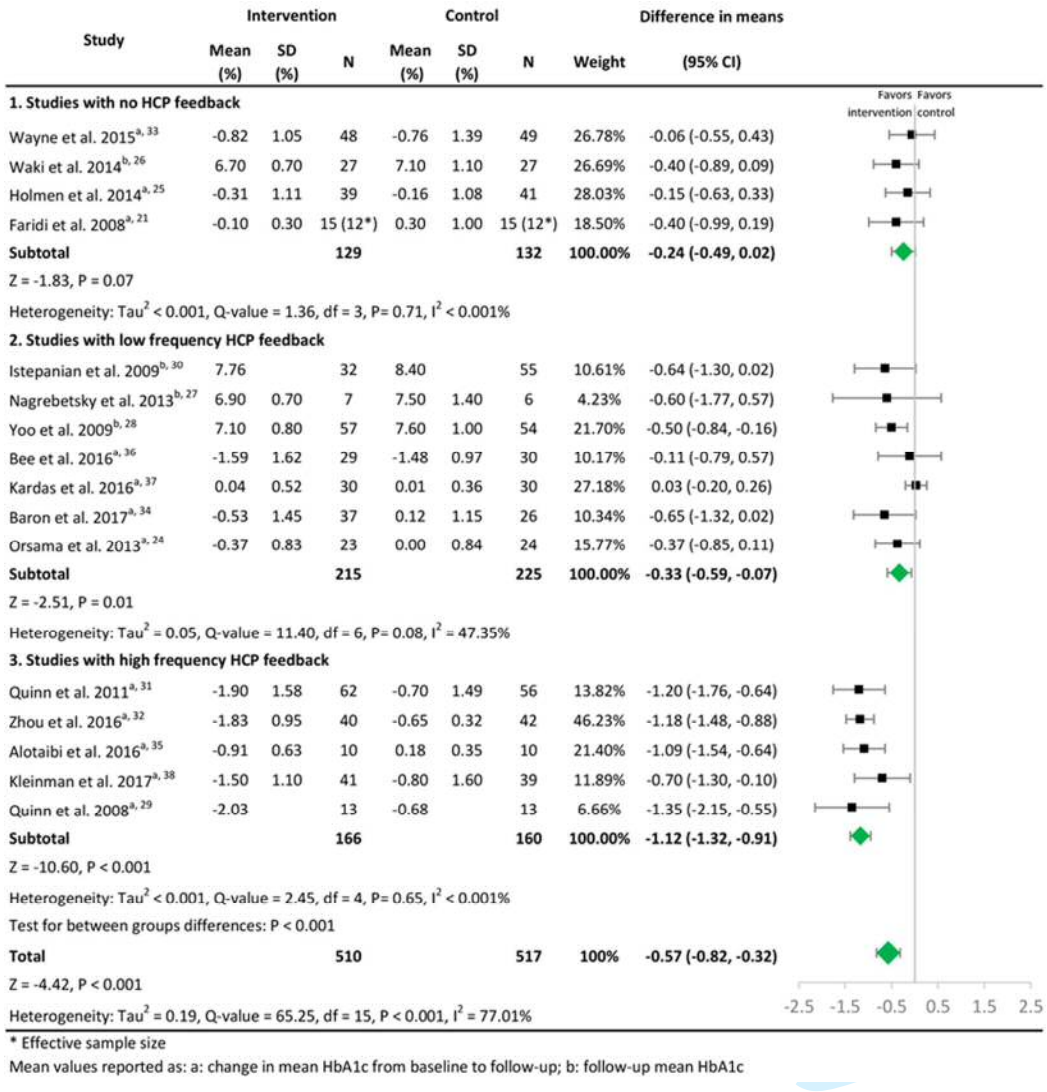

Identification
5211 records identified (search conducted on June 2015)
4467 records identified (search conducted on May 2017)
Screening
7433 records after duplicates removed
7433 records screened
7285 records excluded
116 full-text articles excluded
1. Conference abstracts (n=38)
2. Other interventions (n=31)
3. Ineligible control group (n=3)
4. No relevant outcome reported (n=4)
5. Not an RCT (n=32)
6. Ongoing study (n=4)
7. Participants aged <18 yeas (n=3)
8. Simulated HbA1c (n=1)
Eligibility
148 full-text articles assessed for eligibility
Included
21 studies (32 papers) included in qualitative synthesis
21 studies (32 papers) included in quantitative synthesis (meta-analysis)

Figure 2



Mean values reported as: a: change in mean HbA1c from baseline to follow-up; b: follow-up mean HbA1c

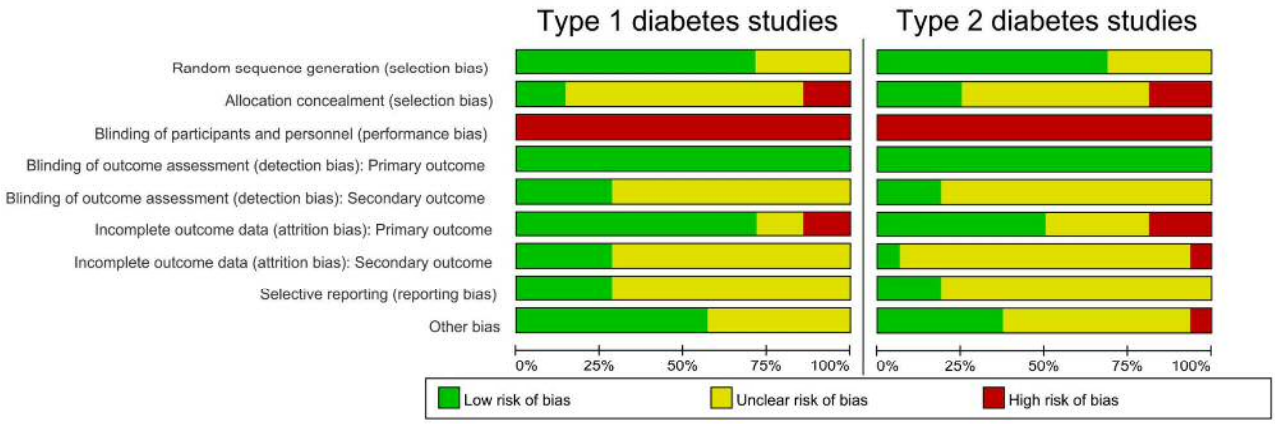
Figure 3



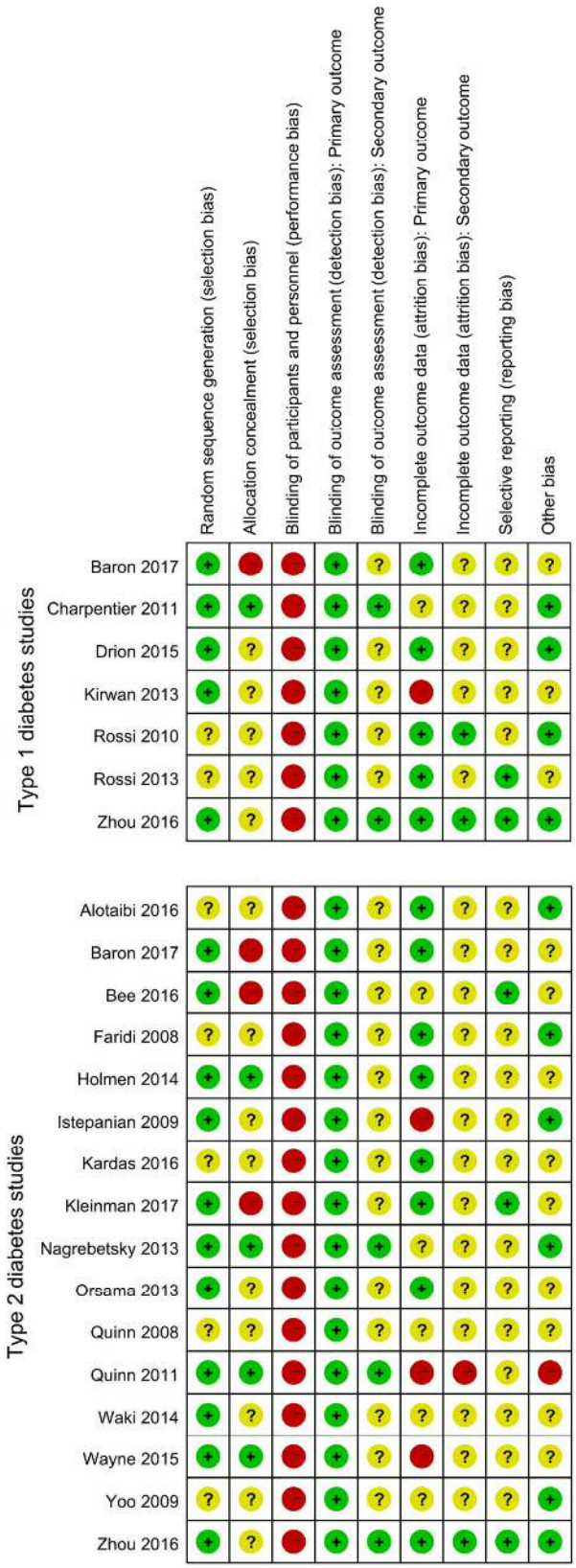
* Effective sample size

Mean values reported as: a: change in mean HbA1c from baseline to follow-up; b: follow-up mean HbA1c

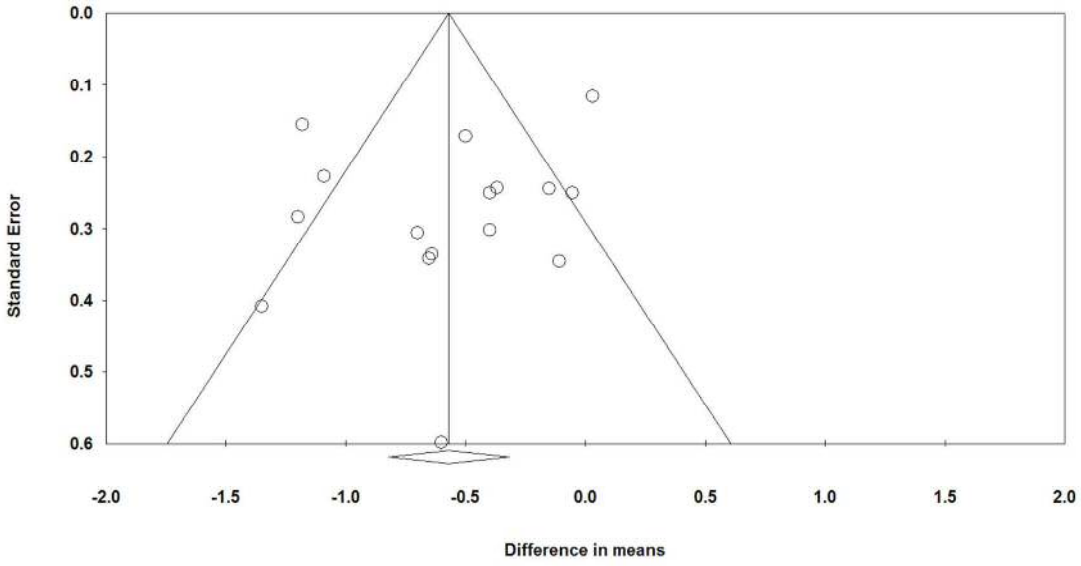
Supplementary Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



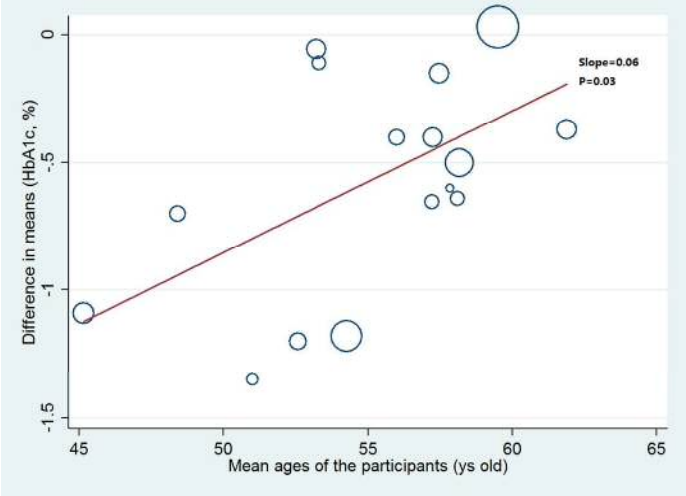
Supplementary Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

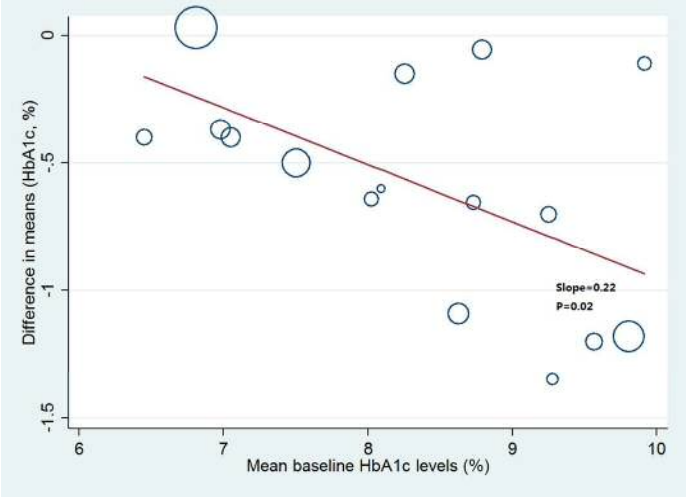


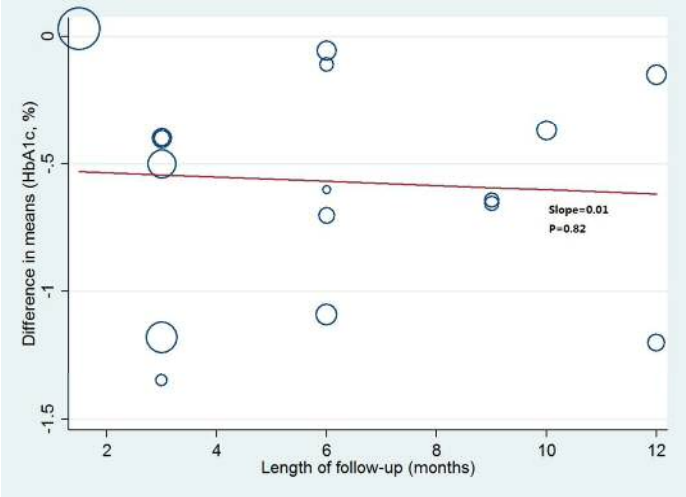
Supplementary Figure 3: Funnel plot of type 2 diabetes studies



Supplementary Figure 4: Univariate meta-regressions of mean ages, mean baseline HbA_{1c} levels and length of follow-up.

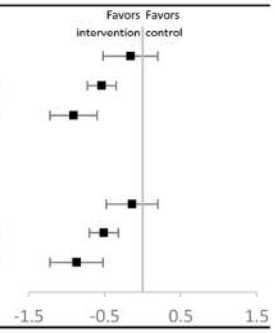






Supplementary Figure 5: Multivariate meta-regressions of HCP feedback after adjustment for mean ages or baseline HbA1c levels

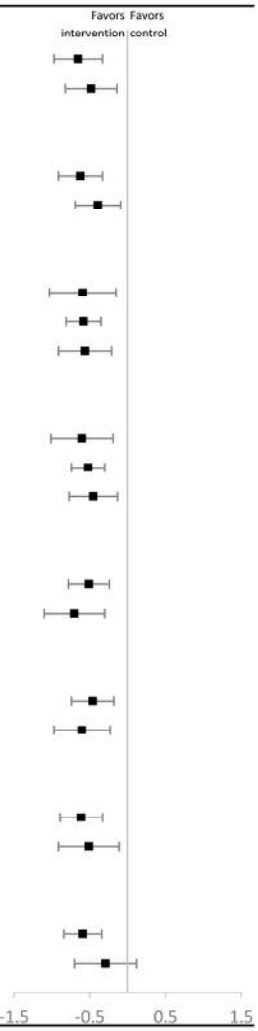
Meta-regression models	Number of studies	Heterogeneity I^2-res	Heterogeneity Tau^2	P-value	Estimated difference in means (95% CI)[#]
HCP feedback (adjusted for mean ages)					
With no HCP feedback	4				-0.16 (-0.52, 0.20)
With low frequency HCP feedback	7	45.85%	0.05	0.01	-0.54 (-0.72, -0.35)
With high frequency HCP feedback	5				-0.91 (-1.23, -0.60)
HCP feedback (adjusted for mean baseline HbA_{1c} levels)					
With no HCP feedback	4				-0.14 (-0.48, 0.20)
With low frequency HCP feedback	7	37.22%	0.04	0.02	-0.51 (-0.69, -0.32)
With high frequency HCP feedback	5				-0.87 (-1.22, -0.52)



[#] The estimated difference in means were derived from meta-regression models given a mean age of 55 years old or a 8.0% mean baseline HbA1c level

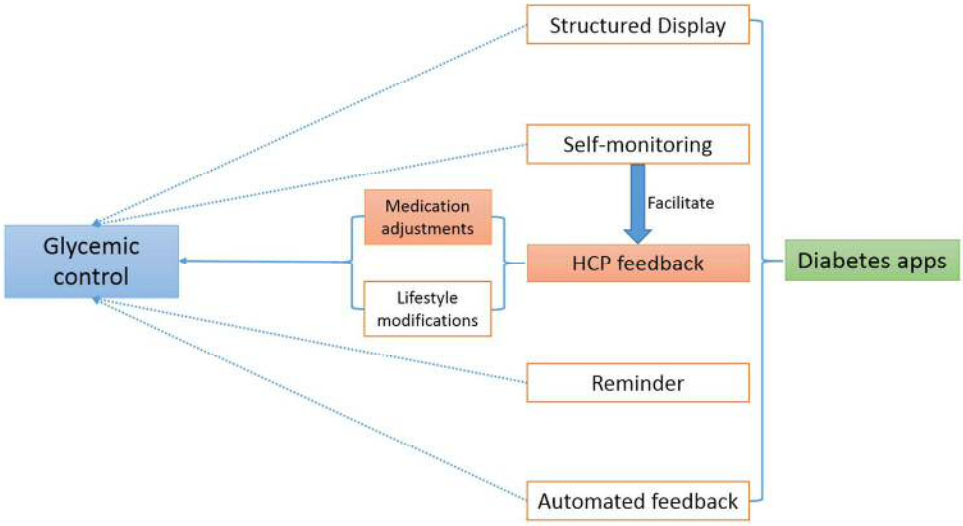
Supplementary Figure 6: Multivariate meta-regressions of the other functions of diabetes apps after adjustment for mean ages or baseline HbA1c levels

Meta-regression models	Number of studies	Heterogeneity I^2-res	Heterogeneity Tau^2	P-value	Estimated difference in means (95% CI)#
Reminder (adjusted for the mean ages)					
With reminder	8	61.12%	0.09	0.5	-0.65 (-0.96, -0.33)
Without reminder	8				-0.48 (-0.83, -0.14)
Reminder (adjusted for the baseline HbA_{1c} levels)					
With reminder	8	48.68%	0.07	0.2	-0.62 (-0.92, -0.33)
Without reminder	8				-0.39 (-0.68, -0.09)
Number of self-monitoring tasks supported (adjusted for the mean ages)					
Supporting only one self-monitoring task	4	66.57%	0.10	0.9	-0.59 (-1.03, -0.15)
Supporting 2-4 self-monitoring tasks	7				-0.58 (-0.81, -0.35)
Supporting >4 self-monitoring tasks	5				-0.56 (-0.92, -0.21)
Number of self-monitoring tasks supported (adjusted for the baseline HbA_{1c} levels)					
Supporting only one self-monitoring task	4	54.26%	0.08	0.6	-0.60 (-1.01, -0.19)
Supporting 2-4 self-monitoring tasks	7				-0.52 (-0.75, -0.30)
Supporting >4 self-monitoring tasks	5				-0.45 (-0.76, -0.13)
Structured display (adjusted for the mean ages)					
With structured display	11	66.33%	0.10	0.4	-0.51 (-0.79, -0.24)
Without structured display	5				-0.70 (-1.10, -0.30)
Structured display (adjusted for the baseline HbA_{1c} levels)					
With structured display	11	56.57%	0.09	0.5	-0.46 (-0.73, -0.18)
Without structured display	5				-0.60 (-0.97, -0.23)
Data entry method (adjusted for the mean ages)					
Wireless data transmission	11	65.16%	0.10	0.7	-0.61 (-0.89, -0.33)
Manual data entry	5				-0.51 (-0.91, -0.11)
Data entry method (adjusted for the baseline HbA_{1c} levels)					
Wireless data transmission	11	53.44%	0.07	0.2	-0.59 (-0.85, -0.34)
Manual data entry	5				-0.29 (-0.70, 0.12)



The estimated difference in means were derived from meta-regression models given a mean age of 55 years old or a 8.0% mean baseline HbA1c level

Supplementary Figure 7: Postulated mechanisms behind the effects of diabetes apps



Supplementary Table 1: Detailed search strategy used in each database.

Data sources	Databases	Search Strategy
OVID	Medline: Ovid MEDLINE(R) 1996 to Present with Daily Update, Ovid MEDLINE(R) Epub Ahead of Print, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations	(mobile.af. or mHealth.af. or exp Cell Phones/ or cellular phone*.af. or exp Smartphone/ or app.af. or apps.af. or exp Mobile Applications/ or iphone*.af. or phone*.af.) and (exp Diabetes Mellitus/ or diabet*.af. or T2DM.af. or T1DM.af. or IDDM.af. or NIDDM.af. or DM.af. or T1D.af. or T2D.af. or MODY.af.)
	EMBASE	
EBSCO	CINAHL Plus	((TX mobile) OR (TX mHealth) OR (TX cellphone*) OR (MM "Cellular Phone+") OR (MM "Smartphone+") OR (TX app) OR (TX apps) OR (MM "Mobile Applications") OR (TX iPhone*) OR (TX phone*)) AND ((MM "Diabetes Mellitus+") OR (TX diabet*) OR (TX T2DM) OR (TX T1DM) OR (TX IDDM) OR (TX NIDDM) OR (TX DM) OR (TX T1D) OR (TX T2D) OR (TX MODY))
Web of Science	Web of Science	(TS=(mobile OR mHealth OR cellphone* OR cellular phone* OR smartphone* OR app OR apps OR mobile application* OR iphone* OR phone*) OR TI=(mobile OR mHealth OR cellphone* OR cellular phone* OR smartphone* OR app OR apps OR mobile application* OR iphone* OR phone*)) AND (TS=(diabetes mellitus OR diabet* OR T2DM OR T1DM OR IDDM OR NIDDM OR DM OR T1D OR T2D OR MODY) OR TI=(diabetes mellitus OR diabet* OR T2DM OR T1DM OR IDDM OR NIDDM OR DM OR T1D OR T2D OR MODY)); Timespan=2015-2017; Search language=Auto
Cochrane	The Cochrane Library	Search all text: mobile OR mHealth OR cellular phone* OR app OR apps OR iphone* OR phone* (#1) MeSH descriptor: [Cell Phones] explode all trees (#2) MeSH descriptor: [Smartphone] explode all trees (#3) MeSH descriptor: [Mobile applications] explode all trees (#4) Search all text: diabet* OR T2DM OR T1DM OR IDDM OR NIDDM OR DM OR T1D OR T2D (#5) MeSH descriptor: [Diabetes Mellitus] explode all trees (#6) (#1 or #2 or #3 or #4) and (#5 or #6) Publication Year from 2015 to 2017

Supplementary Table 2: Baseline characteristics of the included studies and participants

Type 2 diabetes studies

Name (year)	Study design	Length (mths)	Number of participants randomised	Dropped out	Number of participants in the analysis	Imputation methods	Country	Setting	Intervention group(s)	Control group	Inclusion criteria	Exclusion criteria	Study outcomes	Age (years, mean and SD)	Gender (male %)	Duration of diabetes (years, mean and SD)	Treatment regimen	Ethnic groups	Baseline	Post-intervention	Change from baseline	Severe Hypoglycemia (n)
Orsama et al. (2013) (24)	RCT	10	I: 27 C: 29	I: 4 (1 missing value) C: 5	I: 23 C: 24	NA	Finland	Community health center	Patients in the intervention group used Monica to monitor their BP, body weight, physical activity, and BG (for some patients).	Standard medical care	known diagnosis of type 2 diabetes, elevated HbA1c (>6.5%) or currently using oral diabetes medication, age range of 30–70 years combined with HbA1c >6.5%, systolic blood pressure >140mm Hg, or diastolic blood pressure >90mm Hg,	expected poor study compliance (e.g., information technology illiteracy or reluctance to perform self-monitoring), pregnancy, patients with life expectancy of less than 1 year, patients with major elective surgery within the past 6 months or planned for the next 6 months, patients with psychiatric disorders (e.g., depression), or alcohol or narcotics abuse	Primary: HbA1c and systolic and diastolic blood pressure Secondary: body weight Other: Patient acceptance and usability and usefulness of the feedback system	I:62.3 (6.5) C:61.5 (9.1)	I: 54 C: 54	NA	NA	N/A	I: 6.86 (1.56) C: 7.09 (1.51)	N/A	I: -0.37 (0.83) C: 0.00 (0.84)	N/A
Holmen et al. (2014) (25)	RCT	12	FTA: 51 FTA-HC: 50 C: 50	FTA: 11 FTA-HC: 10 C: 9	FTA: 39 FTA-HC: 40 C: 41	NA	Norway	Primary care	FTA: patients used the FewTouch to monitor their food habits, BG, and physical activity. FTA-HC: Group 1 + teleconsulting provided by nurses for the first four months (5 times in total with a mean duration of 20 mins).	Usual care according to clinical guidelines	aged ⩾18 years, had an HbA1c level ⩾7.1% (54.1 mmol/mol), and were capable of completing questionnaires in the Norwegian language, be cognitively able to participate and to use the system and devices provided	NA	Primary: HbA1c Secondary: self-management and health-related quality of life, depressive symptoms, and lifestyle changes	FTA: 58.6 (11.8) FTA-HC: 57.4 (12.1) C: 55.9 (12.2)	FAT: 67 FAT-HC: 50 C: 60	NA	FTA: diet 7% oral agents 44% injections 20% oral and injecton 30%; FTA-HC: diet 4% oral agents 57% injections 15% oral and injecton 23% C: diet 11% oral agents 42% injections 8% oral and injecton 40%	N/A	FTA: 8.1 (1.25) FTA-HC: 8.1(1.05) C: 8.4(1.25)	FTA: 7.8 (1.033) FTA-HC: 8.0 (1.44) C: 8.2 (1.33)	FTA: -0.31 (1.11) FTA-HC: -0.15 (1.36) C: -0.16 (1.08)	N/A
Faridi et al. (2008) (21)	Cluster RCT (2 clinics)	3	I: 15 C: 15	NA	I: 15 C: 15	NA	USA	Community health center	Patients used the app to monitor their BG, exercise, and weight.	Standard diabetes self-managemen	(i) age⩾18 years; (ii) type 2 diabetes diagnosed by a health professional at least 1 year prior and confirmed by other clinical laboratory data (Fasting Plasma Glucose>126 mg dL^{-1} and/or 2-hour 75-g oral glucose tolerance test OGTT>200 mg dL^{-1}; (iii) controlled by either diet or oral medications for at least 3 months; (iv) BMI >25; (v) no exogenous insulin use; (vi) a glycosylated haemoglobin (HbA1c)<8% reflecting fair to good glycemic control; and (vi) serum creatinine<1.5 mg dL^{-1}	NA	Utilization of the system, HbA1c, BMI, blood pressure, physical activity, diabetes self-care and self-efficacy	I:55.3 (8.7) C:56.7 (10.6)	I: 40% C: 33.3%	NA	NA	N/A	I: 6.4 (0.6) C: 6.5 (0.7)	N/A	I: -0.1 (0.3) C: 0.3 (1.0)	N/A
Waki et al. (2014) (26)	RCT	3	I: 27 C: 27	I: 3 C: 2	I: 27 C: 27	Lat observation carried forward	Japan	Hospital	Patients in the intervention group used the DialBetics to monitor their BG, BP, body weight, and activity.	Patients continued their self-care regimen	have any severe complications— serum creatinine below 1.5 mg/dl, or proliferative retinopathy—and had to be able to exercise.	NA	Primary: HbA1c Other: FBS, BP, BMI, LDL-C,HDL-C, and triglyceride, DialBetics's usability, participants' satisfaction	I:57.1 (10.2) C: 57.4 (9.4)	I: 74 C: 78	I: 9.6 (7.0) C: 8.5 (8.0)	I: no medication 26%, oral 48%, noninsulin injection 15%, injection and oral 11% C: no medication 22%, oral 74%, noninsulin injection 0%, injection and oral 4%	N/A	I: 7.1 (1.0) C: 7.0 (0.9)	I: 6.7 (0.7) C: 7.1 (1.1)	N/A	N/A
Nagrebetsky et al. (2013) (27)	RCT	6	I: 8 C: 9	I: 1 C: 3 (1 missing value)	I: 7 C: 6	NA	UK	General practices	Patients in the intervention group used the app to monitor their BG.	Usual care and supportive lifestyle intervention	≥35 years old with type 2 diabetes of at least 3 months' duration and were taking oral glucoselowering medication, ast routinely measured HbA1c ≥64 mmol/mol (8.0%) and <97 mmol/mol (11.0%) with no subsequent records of increase in oral glucose-lowering medication	were unable to follow the trial protocol due to physical, cognitive, or social limitations; were prescribed insulin; or required addition of insulin to treatment regimen, visual impairment, pregnancy or breast feeding, and limited life expectancy or other comorbid conditions making tight blood glucose control inappropriate	HbA1c and changes of oral glucose-lowering medication	I:56 (8) C:60 (13)	I: 71 C: 71	I: 3.0 (0.6-4.7) C: 2.3 (0.4-8.0)	Oral medication: 100%	White: 100%	I: 8.0 (1.0) C: 8.2 (1.2)	I: 6.9 (0.7) C: 7.5 (1.4)	N/A	I: No severe (1 mild hypo) None
Yoo et al. (2009) (28)	RCT	3	I: 62 C: 61	I: 5 C: 7	I: 57 C: 54	NA	Korea	Hospital and community health center	Patients in the intervention group used the app to monitor their BG, BP, exercise, and body weight.	Usual out-patient treatment	diagnosis of both Type 2 diabetes and hypertension at least 1 year previously by a physician; (ii) HbA1c 6.5–10.0%; (iii) blood pressure > 130/80 mmHg; and (iv) body mass index (BMI) ≥ 23.0 kg./m2 (overweight according to Asia-Pacific criteria)	(i) severe diabetic complications; (ii) liver dysfunction with aspartate aminotransferase or alanine aminotransferase > 2.5 times the reference level, or renal dysfunction (serum creatinine > 132 lmol./l); (iii) medical history of congestive heart failure, angina pectoris, myocardial infarction, or stroke based on a physician's diagnosis; (iv) pregnancy or lactation; or (v) othermedical problems that could affect study results or trial participation	Weight; BMI; waist circumference; BP; right baPWV; left baPWV; HbA1c; fasting glucose; HOMA-IR; lipids; triglyceride; adiponectin; hsCRP; interleukin-6	I:57.0 (9.1) C:59.4 (8.4)	I: 64.8 C: 52.6	I: 6.0 (5.4) C: 7.2 (6.0)	NA	NA	I: 7.6 (0.9) C: 7.4 (0.9)	I: 7.1 (0.8) C: 7.6 (1.0)	N/A	not reported in both groups
Quinn et al. (2008) (29)	RCT	3	I: 15 C: 15	I: 2 C: 2	I: 13 C: 13	NA	USA	Community endocrinology and community primary care practice	Patients used the app to monitor their BG, medication dosage, and food intake.	Patients continued usual standards of care	18–70 years old who had a diagnosis of type 2 diabetes for at least 6 months. Study patients were required to have an A1c 7.5% and to have been on a stable diabetes therapeutic regimen for 3 months prior to study enrollment.	NA	Primary: HbA1c Secondary: HCPs' adherence to prescribing guidelines; HCPs ' adoption of the technology Others: Change in medication; diabetes self-care; self-reported control issues	51.0 (11.03)	I: 31 C: 38	I: 7.61 C: 11	I: oral 23%, insulin 31%, injectible non-insulin 46% I: oral 54%, insulin 31%, injectible non-insulin 8%	African American: 62% White: 38%	I: 9.51 C: 9.05	I: 7.48 C: 8.37	I: -2.03* C: -0.68*	N/A
Istepanian et al. (2009) (30)[$]	RCT	9	I: 72 C: 65	I: 40 C: 10	I: 32 C: 55	NA	UK	Hospital	Patients used the app to monitor their BG.	Patients received care from the diabetes center	Ambulant patients aged over 18 years with diabetes	a physical inability to self-monitor blood glucose, pregnancy, severe lifethreatening or terminal illness or an inability to provide written informed consent	Primary: HbA1c	I:60 (12) C:57 (13)	NA	I: 13.3 (8.6) C: 11.7 (8.0)	I: diet 5%, insulin 26%, OHA 47%, OHA and insulin 22% C: diet 5%, insulin 25%, OHA 56%, OHA and insulin 11%	Caucasian: 34% African-Caribbean: 31% Indo-Asian: 31% Other: 4%	I: 7.9 (1.5) C: 8.1 (1.6)	I: 7.76[#] D: 8.4[#]	N/A	N/A

Quinn et al. (2011) (31)	Cluster RCT	12	CO: 38 CPP: 33 CPDS: 80 C: 62	CO: 15 CPP: 11 CPDS: 18 C: 6	CO: 23 CPP: 22 CPDS: 62 C: 56	Linear mixed effect model	USA	Primary care practices	CO: Patients used the app to monitor their BG, diet, and medication CPP: CO + a web-portal allow HCPs to access unanalysed patient data CPDS: CO + a web-portal allow HCPs to access analysed patient data	Patients were provided care as usual	Physician diagnosis of type 2 diabetes for $6 months; Glycated hemoglobin $7.5% within 3 months; Age 18–64 years.	Medicare or Medicaid beneficiaries; Uninsured; Insulin pump users; Not currently managed by study physicians; Pregnant; Active substance, alcohol, or drug abuser (sober ,1 year); Psychotic or schizophrenic under active care; Severe hearing or visual impairment; or No Internet or e-mail access.	Primary: HbA1c Secondary: Depressive symptoms; patient-reported symptoms associated with diabetes; blood pressure; lipids; Hypoglycemic events; hospitalization; emergency room visits	CO: 52.8 (8.0) CPP: 53.7 (8.2) CPDS: 52 (8.0) C:53.2 (8.4)	CO: 52.2 CPP: 45.5 CPDS: 50 C: 50	CO: 7.7 (5.6) CPP: 6.8 (4.9) CPDS: 8.2 (5.3) C: 9.0 (7.0)	NA	Black: 39% White: 53% Other: 8%	CO: 9.3 (1.8) CPP: 9.0 (1.8) CPDS: 9.9 (2.1) C: 9.2 (1.7)	CO: 7.7 (1.0) CPP: 7.9 (1.4 CPDS: 7.9 (1.7) C: 8.5 (1.8)	CO: -1.6 (1.50)[&] CPP: -1.2 (1.47)[&] CPDS:-1.9 (1.58)[&] C: -0.7 (1.49)[&]	None in both groups
Zhou et al. (2016) (32)[$]	RCT	3	I: 40[+] C: 42[+]	I: 0[+] C: 0[+]	I: 40[+] C: 42[+]	NA	China	Hospital	The intervention group installed Welltang on their smart phones and used for diabetes self-management	Patients received usual care once a month	be able to use a smart phone, have no severe complications such as end-phase diabetic nephropathy or proliferative diabetic retinopathy, and be able to exercise	N/A	Primary: HbA1c Second: BG, LDL-C, Weight, BP, hypoglycemic events, satisfaction, diabetes knowledge, self-care behaviors.	I: 55.0 (13.1) C: 53.5 (12.4)	I: 54 C: 60	I: 6.65 (5.14) C: 6.63 (5.06)	I: oral: 26%, insulin: 40%, insulin and oral 34% C: oral: 26%, insulin: 46%, insulin and oral 28%	Chinese: 100%	I: 9.86 (2.38) C: 9.76 (2.51)	I: 7.91 (1.58) C: 8.97(2.08)	I:-1.83 (0.95)[+] C: -0.65 (0.32)[+]	NA
Wayne et al. (2015) (33)	RCT	6	I: 67 C: 64	I: 19 C: 15	I: 48 C: 49	NA	Canada	Primary care clinics	Patients used the app to track key metrics and communicate with health coach at any time in the 24-hour cycle	Patients received health coach support without access to the app	diagnosed with T2DM, if they had an HbA1c ⩾ 7.3% (56.3 mmol/mol) measured within 1 month of consent, and if they were under 70 years of age	N/A	Primary: HbA1c Secondary: weight, BMI, waist circumference, Changes in psychometric assessments	I: 53.1 (10.9) C: 53.3 (11.9)	I: 35 C: 20	NA	NA	Black Caribbean: 40% Caucasian: 27% Hispanic: 9% West Indian: 6% Other: 18%	I: 8.69 (1.32) C: 8.89 (1.30)	I: 7.88 (1.17) C: 8.13(1.27)	I: -0.815 (1.05) C: -0.759 (1.39)	NA
Baron et al. (2017) (34)[$]	RCT	9	I: 41[+] C: 30[+]	I: 4[+] C: 4[+]	I: 37[+] C: 26[+]	NA	UK	Diabetes clinic	Participants allocated to the intervention group were provided with the MTH equipment (BG meter, BP monitor, mobile-phone, and Bluetooth cradle) and training	Standard care	age 18 or above, poorly controlled type 1 or type 2 diabetes (HbA1c≥57.5%)31–33 with the latest HbA1c collected within the last 12 months, taking insulin, and fluency and literacy in English.	Previous experience using MTH, regular extended travels (53 weeks) outside the UK, home visits by a district nurse for BG monitoring and/or insulin administration, a diagnosis of kidney failure or sickle cell disease, pregnancy, and dexterity/visual problems compromising the use of a mobile-phone	Primary: HbA1c Secondary: BP, daily insulin dose, number of DOAs attended Other outcomes: health-related quality of life, symptoms of depression and anxiety	I: 58.2 (13.6) C: 55.8 (13.8)	I: 68.9 C: 42.7	I: 16.5 (8.5) C: 16.9 (6.8)	I: insulin 22.2%, oral and insulin 77.8% C: insulin 31.4%, oral and insulin 71.4%	White: 25% Black: 33% Asian: 36% Other: 6%	I: 8.78 (1.56)[+] C: 8.66 (1.56)[+]	I: 8.29 (1.39)[+] C: 8.91(1.16)[+]	I: -0.53 (1.45)[+] C: 0.12 (1.15)[+]	NA
Alotaibi et al. (2016) (35)	RCT	6	I: 10 C: 10	I: 0 C: 0	I: 10 C: 10	NA	Kingdom of Saudi Arabia	Hospital	Patients were given the SAED system and were trained to operate and run the blood glucose device and to transmit the measurements	Standard care	T2D patients of both genders with an age group between 20–65 years	N/A	HbA1c and the Diabetes knowledge test	I: 44.2 (6.66) C: 46.1 (6.44)	NA	I: 6.2 (3.82) C: 5.7 (3.2)	NA	NA	I: 8.76 (0.76) C: 8.5 (1.45)	I: 7.85 (0.70) C: 8.68 (1.54)	I: -0.91 (0.63) C: 0.18 (0.35)	NA
Bee et al. (2016) (36)	RCT	6	I: 33 C: 33	I: 4 C: 3	I: 29 C: 30	NA	Singapore	Hospital	Patients entered FBG readings into the app daily; the app responded with a suggested insulin dose	Patients in the control group used paper logbooks and written instructions	Insulin-naive T2DMpatientswith suboptimal glycemic control (HbA1c ⩾7.5% [58 mmol/mol]) despite use of two or more oral glucose-lowering drugs	Hypoglycemia unawareness; Severe renal impairment (i.e., eGFR <30 ml/min); Corticosteroid use Serious disease with life expectancy <1 year Pregnancy; Patients with labile medical conditions that would predispose them to poor insulin control (e.g., frequent or recurrent infections); Patients with psychological and social issues that would prevent continuous injection of insulin and monitoring of blood glucose (e.g., major depressive disorder, homelessness)	Primary: HbA1c Secondary: hypoglycemic episodes, Treatment satisfaction, fasting plasma glucose,	53.3 (7.4)	66.70%	12 (8)	Oral: 100%	NA	I: 10.09 (2.06) C: 9.75 (1.37)	I: 8.25 (1.18) C: 8.28 (1.07)	I: -1.59 (1.62) C: -1.48 (0.97)	no episodes of severe hypoglycemia (one confirmed hypoglycemic event: I: 27.3% C: 21.2%)
Kardas et al. (2016) (37)	RCT	1.5	I: 32 C: 30	I: 2 C: 0	I: 30 C: 30	NA	Poland	Primary care	Patients were equipped with COMMODITY12 system, composed of smart phone, and wirelessly connected sensors	Standard care	age 18–65 years, diabetes type 2 diagnosed ⩾6 months prior to the study, currently in the maintenance phase of treatment (of which at least a part consisted of the use of metformin, with a daily dose of ⩾500 mg), and self-committed ability to use the cell phone and the sensors	inter allia, the need to rely on the other persons with drug taking	Primary: system operability and whole trial feasibility Secondary: HbA1c, plasma glucose levels, arterial blood pressure, patient adherence, health-related quality of life	I: 59.9 (5.31) C: 59.0 (8.09)	I: 56.6 C: 63.3	NA	NA	NA	I: 6.78 (1.10) C: 6.84 (0.98)	I: 6.75 (0.95) C: 6.78 (0.92)	0.04 (0.52) 0.01 (0.36)	NA
Kleinman et al. (2017) (38)	RCT	6	I: 44 C: 46	I: 3 C: 7	I: 41 C: 39	NA	India	Diabetes clinic	Intervention was use of Gather Health, an m-Health diabetes management platform	Control participants were instructed to manage their diabetes as usual	Willing to participate and be randomized; Able to speak and read either English, Hindi, Gujarati, or Tamil; Diagnosed with type 2 diabetes for > 6 months; Age 18–65 inclusive, any gender; A1c of 7.5–12.5% (58–113 mmol/mol), inclusive; On stable diabetes therapy for >3 months; Own an Android smartphone; Have not previously used the Gather app	Currently using an insulin pump, continuous glucose monitor, or glucocorticoids; Pregnant or planning to become pregnant in the next 12 months; Received or are planning to receive an organ transplant; Recent major surgery or planning to have major surgery; Active substance, alcohol, or drug abuse (abstinent <1 year); Severe hearing or visual impairment; Significant psychiatric illness, renal disease, hepatic disease, or other disease that impaired ability to complete the study or follow study protocol	Primary: change in A1c from baseline to 6 months Secondary: change in A1c from baseline to 3 months, change in body mass index, waist circumference, blood pressure, fasting BG, lipids, measures of medication adherence, BG testing, communication with doctors, treatment satisfaction, diabetes self-care activities, diabetes distress, self-efficacy, and diabetes knowledge	I: 48.8 (9.0) C: 48.0 (9.5)	I: 82 C: 58.7	I: 10 (median) C: 8.8 (median)	I: orals only 50%, insulin 50% C: orals only 55.1%, insulin 46.3%	NA	I: 9.4 (1.2) C: 9.1 (1.1)	I: 7.9 (1.1) C: 8.2 (1.5)	I: -1.5 (1.1) C: -0.8 (1.6)	NA
I: Intervention; C: Control [#] P=0.06 for between groups difference [$] Studies conducted on mixed populations of type 1 and type 2 diabetes patients (majority of which are type 2) [&] Means and SDs from mixed-effects model [+] For type 2 diabetes patients only (data were additionally provided by corresponding authors) * Pooled SD=2.08 (imputed using Prognostic Method) (15)																					
Type 1 diabetes studies																					
Rossi et al. (2013) (39)	RCT	6	I: 63 C: 64	I: 8 C: 7	I: 63 C: 64	Unstructured correlation	Italy	Diabetes clinics	Patients in the intervention group used DID to calculate the most appropriate dose to be injected at each meal	Standard educational approach based on CHO counting	diagnosis of T1DM, 18 years of age, no previous education on CHO counting, HbA1c levels ‡7.5%, treatment with a basal-bolus regimen with insulin analogs, SMBG measurements at least three times a day, and adequate familiarity in the use of mobile phones according to the physician judgment	treatment with NPH insulin or soluble regular insulin, continuous subcutaneous insulin infusion, insulin regimens other than basal:bolus, eating disorders (based on the physician's judgment), pregnancy/ lactation, inability to send or receive SMSs, inability or unwillingness to give informed consent, or any other disease or condition that could interfere with the compliance with the protocol or the study completion	Primary: HbA1c Secondary: FBG; glucose variability; daily doses of insulin; hypoglycaemic episodes; body weight; lipids; blood pressure Other: Quality of life; patient satisfaction	I: 38.4 (10.3) C: 34.3 (10.0)	I: 46.0 C: 49.1	I: 16.2 (10.0) C: 15.0 (8.4)	I: basal-bolus regimen with insulin analogs: 100% C: basal-bolus regimen with insulin analogs: 100%	N/A	I: 8.4 (0.79)* C: 8.5 (0.80)*	I: 7.9 (0.79)* C: 8.1 (0.80)*	I: -0.49 (0.87)* C: -0.48 (0.88)*	IRR: 1.08 (grade 1) 0.14 (grade 2)

Rossi et al. (2010) (40)	RCT	6	I: 67 C: 63	I: 9 C: 2	I: 67 C: 63	Last observation carried forward	Italy, England and Spain	Diabetes outpatient clinics	Patients in the intervention group used DID to calculate the matching insulin bolus at each meal	Standard carbohydrate counting education	diagnosis of type 1 diabetes, age 18 years, no previous education on carbohydrate counting, and treatment with multiple daily injections of shortacting and long-acting insulin analogs or with continuous subcutaneous insulin infusion; patients practiced self-monitoring of blood glucose at least three times a day; patients were adequate familiarity in the use of mobile phones, according to the physician judgment, and possession of a personal mobile phone card	being treated with NPH insulin or soluble regular insulin, had an eating disorder, were pregnant, were unable to send or receive short text messages, were unable or unwilling to give informed consent, or had any other disease or condition that may interfere with compliance with the protocol or completion of the study	Primary: HbA1c Secondary: FBG, body weight, lipid profile, BP Other: safety related problems, time spent in educational activities, quality of life, patient treatment satisfaction	I: 35.4 (9.5) C: 36.1 (9.4)	I: 44.8% C: 41.0%	I: 17.1 (10.3) C: 15.8 (10.7)	I: Short-acting and/or long-acting analogs 80.6%, Continuous subcutaneous insulin infusion 19.4% C: Short-acting and/or long-acting analogs 80.9%, Continuous subcutaneous insulin infusion 19.1%	N/A	I: 8.2 (0.8) C: 8.4 (0.7)	I: 7.8 C: 7.9	I: -0.4 (0.9) C: -0.5 (1.0)	I: 2 (mild hypoglycemia) C: 2 (mild hypoglycemia)
Charpentier et al. (2011) (41)	RCT	6	G2: 60 G3: 59 C: 61	G2: 4 G3: 2 C: 1	G2: 56 G3: 57 C: 60	Last observation carried forward	France	Hospital	Group 2: Patients used Diabeo to calculate bolus and received two face-to-face follow-up visits. Group 3: Patients used Diabeo to calculate bolus and received teleconsultations by telephone call every two weeks.	Patients kept their paper logbook and attended two follow-up visits	Participants were over 18 years old, had type 1 diabetes for at least 1 year, and had been treated with a basal bolus insulin regimen for at least 6 months, either with MDI or with a pump. HbA1c values during the year before and at entry of the study were at least 8.0%	participation in a diabetes educational program within 3 months before the study or a clinical condition requiring the patient to receive follow-up more frequently than the quarterly visits scheduled	Primary: HbA1c Secondary: patients reaching the HbA1c target of below 7.5%; SMPG frequency; quality of life; Patient satisfaction Other: Major and minor hypoglycaemia episodes	G2: 32.9 (11.7) G3: 31.6 (12.5) C: 36.8 (14.1)	G2: 38.3 G3: 37.3 C: 34.4	G2: 17.6 (8.9) G3: 14.7 (9.1) C: 16.9 (10.5)	G2: Insulin pump 36.7% G3: Insulin pump 36.7% C: Insulin pump 36.1%	N/A	G2: 9.12 (1.01) G3: 8.14 (1.15) C: 8.92 (0.91)	G2: 8.63 (1.07) G3: 8.41 (1.04) C: 9.10 (1.16)	G2: -0.49 (0.89) G3: -0.73 (0.84) C: 0.18 (0.83)	Severe episodes G2: 3 G3: 1 Severe episodes C: 3
Kirwan et al. (2013) (42)	RCT	9	I: 36 C: 36	I: 11 C: 8	I: 25 C: 28	NA	Australia	Diabetes Australia in New South Wales and Queensland	Patients in the intervention group used Glucose Buddy to monitor their BG, insulin dosage, medications, diet, and physical activity.	Patients continued usual care	(1) aged 18-65 years, (2) diagnosed with type 1 diabetes >6 months, (3) HbA1c >7.5%, (4) treated with multiple daily injections or insulin pump, and (5) own a smartphone (iPhone)	pregnant or already using a smartphone application to self-manage their diabetes	Primary: HbA1c Secondary: Diabetes-related self-efficacy; self-care activities; quality of life	I: 36.0 (10.7) C: 34.4 (10.3)	I: 52.8 C: 25	I: 19.7 (9.6) C: 18.2 (9.8)	I: Insulin pump 38.9% C: Insulin pumo 36.1%	N/A	I: 9.08 (1.18) C: 8.47 (0.86)	I: 7.80 (0.75) C: 8.58 (1.16)	I: -1.10 (0.74) C: 0.07 (0.99)	NA NA
Zhou et al. (2016) (32)[$]	RCT	3	I: 10[&] C: 8[&]	I: 0[&] C: 0[&]	I: 10[&] C: 8[&]	NA	China	Hospital	The intervention group installed Welltang on their smart phones and used for diabetes self-management	Patients received usual care once a month	be able to use a smart phone, have no severe complications such as end-phase diabetic nephropathy or proliferative diabetic retinopathy, and be able to exercise	N/A	Primary: HbA1c Second: BG, LDL-C, Weight, BP, hypoglycemic events, satisfaction, diabetes knowledge, self-care behaviors.	NA	NA	NA	NA	Chinese: 100%	NA	NA	I: -2.24 (1.05)[&] C: -1.52 (1.14)[&]	NA
Drion et al. (2015) (43)	RCT	3	I: 31 C: 32	I: 1 C: 0	I: 31 C: 32	Not reported	Netherland	Hospital	Patients in the intervention group were asked to use the DBEES application and a personal web portal linked to the DBEES application	Patients kept their paper diary	owned a smartphone (other than a BlackBerry) and were familiar with its use; over 18 years old, had T1DM, and were treated with multiple daily injections (MDI), continuous subcutaneous insulin infusion (CSII), or continuous intraperitoneal insulin infusion (CIPII)	had used a diabetes application in the 3 months prior to their visit, did not have internet or email access, or were unable to read Dutch	Primary: QOL Secondary: diabetes-related distress, HbA1c, daily frequency of SMBG, usability of DBEES system	I: 33 C: 35	I: 65 C: 63	I: 18 (17) C: 15 (14)	I: continuous subcutaneous insulin infusion 65%, multiple daily injections 35% C: continuous subcutaneous insulin infusion 66%, multiple daily injections 34%	N/A	I: 8.01 (1.65) C:7.55 (1.28)	I: 7.88* C: 7.91*	I: -0.13[#] C: 0.36[#]	NA
Baron et al. (2016) (34)[$]	RCT	9	I: 4[&] C: 6[&]	I: 1[&] C: 1[&]	I: 3[&] C: 5[&]	NA	UK	Diabetes clinic	Participants allocated to the intervention group were provided with the MTH equipment (BG meter, BP monitor, mobile-phone, and Bluetooth cradle) and training	Standard care	age 18 or above, poorly controlled type 1 or type 2 diabetes (HbA1c57.5%)31–33 with the latest HbA1c collected within the last 12 months, taking insulin, and fluency and literacy in English.	previous experience using MTH, regular extended travels (53 weeks) outside the UK, home visits by a district nurse for BG monitoring and/or insulin administration, a diagnosis of kidney failure or sickle cell disease, pregnancy, and dexterity/visual problems compromising the use of a mobile-phone	Primary: HbA1c Secondary: BP, daily insulin dose, number of DOAs attended Other outcomes: health-related quality of life, symptoms of depression and anxiety	NA	NA	NA	NA	NA	I: 11.88 (3.16)[&] C: 9.99 (2.14)[&]	I: 11.47(3.38)[&] C: 9.48(1.98)[&]	I: 0 (1.44)[&] C: -0.41 (2.37)[&]	NA

I: Intervention; C: Control
* SDs were calculated from SEs or 95% CIs
# Pooled SD=2.27 (imputed using Prognostic Method)
& For type 1 diabetes patients only (data were additionally provided by corresponding authors)
$ Studies conducted on mixed populations of type 1 and type 2 diabetes patients
* Means were imputed from median,q1 and q3 (16)

Supplementary Table 3: Characteristics of the apps in the included studies

Type 2 diabetes studies

Name (year)	App used in the study	Self-monitoring tasks	Data entry method	CHO/insulin bolus calculator	Medication adjustment support	Real-time personalized feedback	Structured display	HCP feedback	Freq. of HCP feedback	Categories of freq. of HCP feedback	Other functionalities	Feedback received
Orsama et al. (2013) (24)	Monica	BG, BP, body weight, and physical activity (pedometer)	All data were manually imputed	NO	NA	YES	YES	YES	When necessary (study nurses scanned through patients' status each week)	Low frequency	NA	1. Real-time graph display reflecting the uploaded data in relation to individual target value generated by app. 2. Automatically generated, theory-based, health promotion-rich information, motivation, and behaviour skills feedback messages, linked to patients' remote reports of their health parameters. 3. Study nurses scanned through the status of all intervention patients each week and contacted patients if warranted by their remote data reports. 4. A web portal (Medinet) enabled participants to view their uploaded data.
Holmen et al. (2014) (25)	FewTouch	Food habits registration, BG, and physical activity	BG data were automatically transferred to the app; activity data and food habits were entered manually	NO	NO	NO	YES	NO	NA	No HCP feedback	Personal goal setting system, general diabetes education system	1. Real-time feedback from the app on how the individually set goals were met within the defined period. 2. Motivational feedback through symbols such as smiling faces and colour codes in the app. 3. Patients can also access related tips and look up words and concepts related to their diseases.
Faridi et al. (2008) (21)	NICHE	BG, exercise (pedometer) and weight	BG and weight data were automatically transmitted (indirectly); pedometer counts were manually entered	NO	NO	YES	YES	NO	NA	No HCP feedback	NA	1. Real-time, automated, graphical and texts feedback and reminders based on patient-specific data. 2 .Upon receipt of newly submitted patient data, the Confidant server software will generate and send one or more feedback messages directly to the patient's cell phone. 3. A web-based portal for patients and clinicians to view measurement data and prior messages received from the system.
Waki et al. (2014) (26)	DiaBetics	BG, BP, body weight and pedometer counts, voice/text messages about meals and exercise, photos of meals	BG,BP, body weight and pedometer data were transmitted automatically to the app; meals and exercise were input by voice/text message or photos	NO	NA	YES	YES	YES	When necessary (no readings were defined as abnormal, a health care provider's time was not required)	No HCP feedback	The database triggered alerts for missed or late readings (reminder)	1. Data were automatically evaluated following the Japan Diabetes Society (JDS) guideline's targeted values, DialBetics determined if each reading satisfies guideline requirements, then immediately sent those results to each patient's smartphone. 2. Readings defined as abnormal were reported to a doctor as "Dr Call," meaning a physician will check the data and interact with the patient if necessary. 3. Voice input was converted to text and matched with text in the DialBetics database; advice on lifestyle modification, matched to the patient's input about food and exercise, was sent back to each patient immediately after the patient's input. 4. Patients' photos of meals were sent to the server; the nutritional value of those meals was calculated by dieticians, then sent back to each patient. 5. Patients can view their measurement data as well as graphic outputs of their measurements with diet and exercise history.
Nagrebetsky et al. (2013) (27)	t+Diabetes	BG	BG data were automatically transmitted to the app	NO	NA	NO	YES	YES	Monthly	Low frequency	NA	1. Real-time graphical feedback on glucose levels. 2. BG reading were also monitored by research nursing twice a week via a web-based portal, and support and encourage patients using standardized text messages and telephone calls monthly. 3. Patients used the phone application to review their glucose levels every 3 weeks and, if necessary, titrate their oral glucose-lowering medication.
Yoo et al. (2009) (28)	Ubiquitous Chronic Disease Care	BG, BP, exercise, and body weight	BG data were automatically transmitted to the app; BP and weight data were manually entered	NO	NO	YES	NO	YES	When necessary	Low frequency	Reminder	1. Real-time automated SMS feedback of encouragement, reminders, and recommendations according to the data input. 2. Participants received information via SMS three times a day regarding healthy diet and exercise methods, along with general information about diabetes, hypertension and obesity. 3. A web-based portal for physicians to view patient data and send individualized recommendations to patients when needed.
Quinn et al. (2008) (29)	Diabetes Manager	BG, medication dosage and carbohydrates intake	BG data were automatically sent to the app, other data were manually input	NO	NA	YES	NO	YES	When necessary (by study team) plus feedback from HCP every four weeks	High frequency	Direct patients to test BG at optimal times (reminder)	1. Real-time feedback about the BG level related to the patient-specific target level and was shown HCP-prescribed medication instruction. 2. If BG levels were above or below target levels, patients received real-time feedback on how to correct the BG level. 3. Data were sent to server and analysed by automated algorithms and research team; patients would receive positive feedback if no problems detected; if problems detected, patients were given further feedback and education, or even referral if needed. 4. Suggestions of medical changes to patients (approved by HCP first). 5. HCPs were provided with logbook to review, attached with analysis of the patient data and trend.
Istepanian et al. (2009) (30)[$]	Not specified	BG	Automatically transmitted to the app	NO	YES	NO	NO	YES	Low level contact	Low frequency	The mobile phone alerted the patient when a measurement was due (reminder)	1. The research clinicians reviewed the recordings via a web-based application. Letters were sent from the clinician to the patients and their general practitioners with details of the amalgamated readings and treatment recommendations.
Quinn et al. (2011) (31)	Diabetes Manager	BG, carbohydrates consumed, diabetes medications taken, and miscellaneous comments regarding diabetes self-care	BG data were automatically sent to the app, other data were manually input	NO	NA	YES	NO	YES	Average one phone call per month plus intermittently electronic messages (from every week to every 2-3 months)	High frequency	Learning library	1. Real-time educational, behavioural and motivational feedback regarding patients input data, trend of recent entered data and physicians' medication instruction. 2. Patients and PCPs had access to a web-portal consisted of secure messaging centre (for patient-provider communication), personal health record with additional diabetes information, learning library and logbook to review historical data (analysed data). 3. Diabetes educators intermittently reviewed patient data and communicated with patients electronically or via phone (frequency: high risk level patents: at most 4 times a month; others every 2-3 months).

Zhou et al. (2016) (32)[$]	Welltang	BG, carbohydrate intake, medications, physical activity, blood pressure, and weight/height	Data were manually entered	NO	YES	NO	YES	YES	Every one to two weeks; average 3-10 min of time spent ; mean number of contacts was 11 (once every week)	High frequency	General diabetes education system; alerts for missed readings and a diabetes forum	1. Real-time graphical feedback on glucose levels. 2. The study team provided feedback on the blood glucose levels of patients, their target goals, and their individualized medication regimens based on the data they entered once a week or every 2 weeks. 3. Readings outside threshold limits would automatically trigger a message to be sent to patients and notify clinicians. 4. Patients received an electronic action plan as pre-visit summaries for physician office visits once a month.
Wayne et al. (2015) (33)	NexJ Health Coach+	BG, exercise, food intake, weight/BMI and mood	Data were manually entered	NO	NA	NO	YES	YES	Average 37 minutes/week of interaction (39 minutes/week of interaction in the control group)	No HCP feedback	Reminder and health library	1. Real-time graphical feedback on patient reported data. 2. The HC co-monitored the client's mobile phone input and directed immediate attention (on a 24-hour/day and 7-day/week basis) to episodes of desirable progress, relapse, and resistance. 3. Patients could communicate with their health coach at any time in the 24-hour cycle via secure messaging, scheduled phone contact, and/or during in-person meetings.
Baron et al. (2017) (34)[$]	Not specified	BG, BP, physical activity, insulin dose and weight	BG and BP data were automatically transmitted, other data were manually entered	NO	YES	NO	YES	YES	When necessary plus six weekly educational calls	Low frequency	N/A	1. Colour-coded graphical feedback on the data recorded was automatically displayed following each data transfer. 2. MTH nurses provided feedback on out-of-range clinical readings (as needed). 3. MTH nurses made six weekly educational calls to deliver diabetes education. 4. MTH nurses supported insulin titration.
Alotaibi et al. (2016) (35)	SAED	BG	BG data were automatically transmitted	NO	YES	YES	YES	YES	Patient can send messages to HCP at any time, HCP monitored and reviewed patients' condition and advice on treatment	High frequency	General diabetes education system and computerized alerts and reminders	1. The medical staff monitored and reviewed the patient's condition using the data collected and stored in the database to plan and advice on the treatment. 2. Based on the blood glucose and HbA1c readings from the database, automated feedback was securely transmitted in real-time to the patients' smart phone. 3. SMS education program wherein the patients received weekly messages to keep them informed about diabetes and other related information. 4. Real-time graphical feedback on patient reported data.
Bee et al. (2016) (36)	Diabetes Pal	BG	Data were manually entered	YES	YES	NO	YES	YES	When necessary (hypoglycaemic episodes)	Low frequency	General diabetes education system	1. Patients in the intervention group entered FBG readings into the app daily; the app responded with a suggested insulin dose 2. An administrative module where the research staff could remotely monitor glucose readings submitted and flag issues to the endocrinologists. 3. Generates graphs from the daily readings, so patients can see their progress in managing their diabetes.
Kardas et al. (2016) (37)	COMMODITY12	BG, ECG, heart rhythm, respiratory movements, activity, weight, BP and adherence	Data were automatically transmitted	NO	YES	YES	NO	YES	When necessary (hypo- and hyperglycaemic episodes)	Low frequency	N/A	1. Artificial Intelligence Layer (AIL) proved to produce alerts according to the relevant algorithms for cases of hypo- and hyperglycaemia, tachy- and bradycardia cases, as well as the supposed risk of the sleep apnoea. These alerts were presented in the system, and made ready for use by clinicians. 2. The data are interpreted by personal agents that use expert biomedical knowledge to derive important insights about the individual's health status, which are then presented in the form of active feedback to the patient directly from the device, or via health professionals who assist in diagnosis, treatment and life management. 3. Real-time graphical feedback on patient reported data.
Kleinman et al. (2017) (38)	Gather Health	BG, medication	Data were manually entered	NO	NA	NO	YES	YES	sent 497 messages to providers, and received 890 messages from providers.	High frequency	The app automatically reminded participants to complete tasks each day (reminder)	1. BG tests submitted out of standard ranges had automated question follow-up to identify issues, and participants could message questions to providers. Each site's health coach regularly responded to patient questions and systemgenerated alerts. 2. Provider contact with participants outside the system was discouraged, except in cases of high-risk glycemic data or technical troubleshooting. 3. Real-time graphical feedback on patient reported BG data.
[$] Studies conducted on mixed populations of type 1 and type 2 diabetes patients (majority of which are type 2)												
Type 1 diabetes studies												
Rossi et al. (2013) (39)	Diabetes Interactive Diary	BG, food intake (CHO and calories), dose of insulin, physical activities, and specific events	Data were manually entered	YES	YES	NO	NO	YES	Every one to three weeks; average 0.8 message exchanged per week	High frequency	Food exchange, prevention of compliance	1. CHO/insulin bolus calculator: DID can automatically calculate the most appropriate insulin dose on the basis of entered BG, food intake (CHO and calories) and current insulin dose, and predefined carbohydrate-to-insulin ratio and the glycaemic correction factor, together with other information already filled out in the DID (e.g., physical activity, glycaemic target, insulin dose, and specific events). 2. All the recorded data were sent to the physician on average each 1–3 weeks. Any new therapeutic and behavioural prescriptions were sent from the diabetes clinic computer to the patient's mobile phone.
Rossi et al. (2010) (40)	Diabetes Interactive Diary	BG, dose of insulin injections, food intake, physical activity, and specific events	Data were manually entered	YES	YES	NO	NO	YES	Average 2 meesages per week sent to the physician	High frequency	Food exchange, prevention of compliance	1. CHO/insulin bolus calculator: DID can automatically calculate the most appropriate insulin dose on the basis of entered BG, food intake (CHO and calories) and current insulin dose, and predefined carbohydrate-to-insulin ratio and the glycaemic correction factor, together with other information already filled out in the DID (e.g., physical activity, glycaemic target, insulin dose, and specific events). 2. Data stored in the mobile phone are periodically sent to the personal computer of the physician. Then, any new therapeutic and behavioural prescription can be sent from the computer to the mobile phone.
Charpentier et al. (2011) (41)	Diabeo	BG, carbohydrate intake and physical activity	Data were manually entered	YES	YES	NO	NO	NO	NA	No HCP feedback	plasma glucose targets	1. Bolus calculators using validated algorithms, taking into account carbohydrate intake, pre-meal blood glucose, and anticipated physical activity reported by the patient. 2. Automatic algorithms for the adjustment of carbohydrate ratio and basal insulin or pump basal rates when the postprandial or fasting plasma glucose levels are off target 3. Data transmission to medical staff computers to allow easy telemonitoring and teleconsultations

Kirwan et al. (2013) (42)	Glucose Body	Blood glucose levels, insulin dosages, other medications, diet (food item in grams), and physical activities (minutes)	Data were manually entered	NO	NA	NO	YES	YES	First 6 months: approximately 2 text messages per patient per week; 5 minutes per patient (n=36) per week	High frequency	N/A	1. Patients can view their data on a customizable graph. 2. Data were reviewed by an educator and all patients in the intervention arm were sent a minimum of 1 personalized text-message communication per week for the first 6 months of the study.
Zhou et al. (2016) (32)[$]	Welltang	BG, carbohydrate intake, medications, physical activity, blood pressure, and weight/height	Data were manually entered	NO	YES	NO	YES	YES	Every one to two weeks; average 3-10 min of time spent ; mean number of contacts was 11 (once every week)	High frequency	general diabetes education system; alerts for missed readings and a diabetes forum	1. Real-time graphical feedback on glucose levels. 2. The study team provided feedback on the blood glucose levels of patients, their target goals, and their individualized medication regimens based on the data they entered once a week or every 2 weeks. 3. Readings outside threshold limits would automatically trigger a message to be sent to patients and notify clinicians. 4. Patients received an electronic action plan as pre-visit summaries for physician office visits once a month.
Drion et al. (2015) (43)	DBEES	BG, carbohydrate intake, medication and physical exercise	Data were manually entered	NO	NO	NO	YES	NO	N/A	No HCP feedback	Alerts and reminders, a diabetes forum	1. Allows patients to use a number of charts and statistics that can visualize the recorded information. 2. Data recorded can be made available to diabetes nurses.
Baron et al. (2016) (34)[$]	Not specified	BG, BP, physical activity, insulin dose and weight	BG and BP data were automatically transmitted, other data were manually entered	NO	YES	NO	YES	YES	When necessary plus six weekly educational calls	Low frequency	N/A	1. Colour-coded graphical feedback on the data recorded was automatically displayed following each data transfer. 2. MTH nurses provided feedback on out-of-range clinical readings (as needed). 3. MTH nurses made six weekly educational calls to deliver diabetes education. 4. MTH nurses supported insulin titration.

[$] Studies conducted on mixed populations of type 1 and type 2 diabetes patients

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Mobile phone applications and self-management of diabetes: a systematic review and meta-analysis of randomised trials

Ben Carter, Jiayuan Li, Can Hou, Qian Xu

Citation

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Review question

The aim of this systematic review is to update the evidence of the effect of mobile phone applications (apps) on glycemic control (HbA1c) in the self-management of diabetes and explore the factors that may influence the efficacy of apps on glycemic control.

Searches

In the previous study, we searched relevant studies that were published between 1 January 1996 and 1 June 2015 from five databases: Medline, CINAHL, Cochrane Library, Web of Science, and Embase. For details of the search strategy used, please refer to: "Do Mobile Phone Applications Improve Glycemic Control (HbA1c) in the Self-management of Diabetes? A Systematic Review, Meta-analysis, and GRADE of 14 Randomized Trials." Diabetes Care 39.11 (2016): 2089-2095. In this systematic review, we will update the searches in Medline, CINAHL, Cochrane Library, Web of Science, and Embase databases to find relevant studies that were published between 2015 and 2017. The search strategy used will be slightly modified to reflect some research progress in this area. The following terms and medical subject headings (MeSH) were used during the search: (mobile OR mHealth OR cellphone* OR MeSH “Cellular Phone” OR MeSH “Smartphone” OR app OR apps OR phone* OR iphone* OR MeSH “Mobile Applications”) AND (MeSH “Diabetes Mellitus” OR diabete* OR T2DM OR T1DM OR IDDM OR NIDDM OR DM OR T1D OR T2D OR MODY). The references of the included studies will also be hand searched to identify any additional articles.

Types of study to be included

Only the studies that evaluated the effect of diabetes mobile phone apps on diabetes self-management and adopted a randomised controlled trial (RCT) design will be included.

Condition or domain being studied

Diabetes mobile phone applications (diabetes apps) is a newly emerging technology for diabetes self-management. Due to its ubiquitous, low-cost, interactive, and dynamic health promotion, there is potential for diabetes apps to provide an effective intervention in diabetes self-care. Our previous systematic review with GRADE of the evidence demonstrated that diabetes apps could help type 2 diabetes patients to control HbA1c (Hou et al., 2016). This conclusion is also supported by a recent systematic review (Wu et al., 2017). However, several questions still remain to be answered:

1) Do diabetes apps improve glycemic control among type 1 diabetes patients?

2) What functions of the apps are associated with better efficacy?

3) Are there any other factors that may influence the effect of diabetes apps?

4) What is the evidence that using diabetes apps is safe for diabetes patients?

Participants/population

The participants were over 18 years old and had type 1 or type 2 diabetes. The self-management of participants aged younger than 18 years largely relies on their parents. Therefore, studies with participants age younger than 18 years were not included.

Intervention(s), exposure(s)

We define diabetes apps as mobile phone software that accepts data (transmitted or manual entry) and provides feedback to patients on improved management (automated or by health care professional [HCP]).

Comparator(s)/control

The control group in the study received usual diabetes care without any telehealth program(s) linked to the management of diabetes.

Context

Primary outcome(s)

The primary outcome of interest will be HbA1c.

Secondary outcome(s)

The secondary outcome will be severe hypoglycemia events reported. Studies included should report either HbA1c as outcome or report hypoglycemia events in both intervention and control groups.

Data extraction (selection and coding)

Data will be extracted from each included study by one author (CH) and verified by a second author. Disagreement will be resolved by discussion with a third author (BC or Jiayuan Li). The following data will be extracted: author name, year of publish, study design, study length, setting, intervention group, control group, number of participants randomised, number of participants withdrew, number of participants in the analysis, imputation method, number of males and females, age, duration of diabetes, treatment regimen, ethnic group, baseline HbA1c, post-intervention HbA1c, HbA1c change from baseline, hypoglycemia, app used in the study, self-monitoring tasks supported, data entry method, and functions of the app (including CHO/insulin bolus calculator, number of self-monitoring tasks supported, medication adjustment support, structured feedback, target setting, reminders, HCP feedback, HCP feedback frequency and other functionalities).

Risk of bias (quality) assessment

Risk of bias will be independently evaluated by two authors using the Cochrane risk of bias tool and discussed if needed by a third. Risk of bias will be assessed in the following domains: selection bias, performance bias, detection bias (primary and secondary outcomes), attrition bias (primary and secondary outcomes), reporting bias, and other bias (Higgins and Green, 2011). A third reviewer resolved any discrepancies in bias coding. Studies will not be excluded on the basis of risk of bias. Studies will be categorized as 'low risk of bias', high risk of bias, or 'unclear'.

Strategy for data synthesis

Measure of treatment effect

For primary outcome, the treatment effect will be either mean difference in HbA1c or mean HbA1c at follow-up, but mean difference in HbA1C is preferred.

For secondary outcome, the treatment effect will be risk ratios (RR).

Dealing with missing data

When required data is missing, we will first try to contact the corresponding authors of the studies. When necessary, we will use specific statistical methods to calculate missing data (Ma et al., 2008).

Meta-analysis

All the analyses will be conducted separately for type 1 and type 2 diabetes studies.

For primary outcome, pooling will be carried out using an inverse variance random effects model for type 1 and type 2 diabetes studies separately (DerSimonian and Laird, 1986). Heterogeneity will be assessed and quantified using the I2 statistic. An I2 of 0% to 40% might represent no important heterogeneity, 30% to 60% might represent moderate heterogeneity, 50% to 90% might represent substantial heterogeneity and 75% to 100% might represent considerable heterogeneity. When substantial heterogeneity is found (I2>50%), we will try to explore the source of heterogeneity.

For secondary outcome, pooling will be carried out using DerSimonian & Laird random effects model with the estimate of heterogeneity being taken from the Mantel-Haenszel model (Mantel and Haenszel, 1959).

If studies were conducted on mixed participants with type 1 and type 2 diabetes, we will first contact the corresponding authors of the studies for additional data. If additional data is not available, the studies will be assigned to either type 1 or type 2 diabetes group according to the percentage of participants with type 1 and 2 diabetes.

For studies with multiple intervention groups, only the intervention group that are relevant to meta-analysis will be selected. If more than two groups are relevant, we will combine the groups to create a pair-wise comparison.

For cluster randomised controlled trial, effect size extracted from an analysis that properly accounts for the cluster design is preferred. Otherwise, an effective sample size will be used instead: Neffective= (k*m)/(1+(m-1)*ICC), where k indicates the number of clusters; m, the number of observations per cluster; and ICC, the intracluster correlation coefficient.

Analysis of subgroups or subsets

Based on our previous study, a small number of type 1 diabetes studies is anticipated. Therefore, we will only carry out few subgroup analyses on studies with type 1 diabetes to explore heterogeneity. The following

subgroup analyses will be carried out: by length of the study follow up (less than one month, between one and six months, and greater than 6 months), and by functions of the apps (with CHO/insulin bolus calculator vs without CHO/insulin bolus calculator, with HCP feedback vs without HCP feedback).

For type 2 diabetes studies, univariate meta-regression will be conducted first by length of the study follow up, baseline HbA1c level, age of the participants and medication regimen. Effects that found to be statistically significant ($p<0.1$) will be included in the next multivariate meta-regression. A multivariable meta-regression will then be conducted using restricted maximum likelihood (REML) random effect model (Van Houwelingen et al., 2002). This model will be used to explore which functions of the apps (HCP feedback, number of self-monitoring tasks supported, structured feedback, reminders, and data entry method) are associated with better efficacy after adjusting for effects that found to be statistically significant in the univariate meta-regression. I-squared –residual in the multivariate meta-regression will be calculated to reflect residual heterogeneity.

Meta-analyses and meta-regression will be conducted using the STATA (Version 14.0).

Sensitivity analysis

For primary outcome, sensitivity analyses will be carried out by removing studies with high risk of bias, changing the parameter ICC for cluster RCTs, changing the method of missing data imputation and removing studies conducted on mixed participants.

For secondary outcome, sensitivity analyses will be carried out by changing the statistical model to the Mantel and Haenszel and the inverse variance fixed effect model (Higgins and Green, 2011).

Publication bias

A funnel plot will be used to visually inspect publication bias where 10 or more studies are pooled (Higgins and Green, 2011).

Independent participant meta-analysis

Authors of all included studies will be contacted and asked to provide the individual data to carry out an individual participant meta-analysis (Riley et al., 2010). The outcomes will be analysed as per the traditional meta-analysis, however studies will be fitted as random effects and important and consistent covariates included will include: patient age; gender, and group allocated. As per previous analyses, the analyses will be carried out separately for type 1 and type 2 diabetes. All analyses will be carried out in Stata 14.

Contact details for further information

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Anticipated or actual start date

01 May 2017

Anticipated completion date

01 August 2017

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Conflicts of interest

None known

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English

Country

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Stage of review

Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Cell Phones; Diabetes Mellitus; Humans; Mobile Applications; Self Care

Date of registration in PROSPERO

24 May 2017

Date of publication of this version

25 May 2017

Revision note for this version

Joint corresponding authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Revision note

Joint corresponding authors

Versions

25 May 2017

24 May 2017

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	PROSPERO CRD42017067774
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Supplementary Table 2 and 3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 7-8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplementary Table 2 and 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Figure 1 and 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2 and 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 11-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 13-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097